Neural correlates of emotion dysregulation in borderline personality disorder and their implications for psychotherapeutic treatment

Cumulative Doctoral Thesis

Presented to the Faculty of Arts and Social Sciences
of the University of Zurich

for the degree of Doctor of Philosophy

by

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Accepted in the Fall Semester 2014
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Zurich, 2014

ACKNOWLEDGEMENTS

I would like to thank my supervisors Prof. Dr. Lutz Jäncke and Prof. Dr. Uwe Herwig for providing me the opportunity to undergo my PhD studies in such an interesting field of sciences. I thank them for their mentoring and scientific guidance as well as for their stimulating discussions and constructive criticism.

I also would like to express my thanks to PD Dr. Annette B. Brühl for her competent advisory and skilled support, especially in methodological and statistical issues. I am also thanking Dr. Philipp Stämpfli for his guidance and mentoring in all technical aspects regarding the fMRI method. Further thanks go to my co-workers, particularly to Sarah Opialla, for creating an enjoyable working atmosphere.

Special thanks go to Dr. Volker Baur for the fruitful discussions and the very much needed coffee breaks.

I am also very thankful to Prof. Dr. Boris B. Quednow for his support and for being part of the PhD committee.

My deepest thanks go out to my family, who continuously showed me love, encouraged me and supported me throughout all the different phases of my dissertation.

Last, but not least, I am very grateful to all subjects, who participated in the studies.

TABLE OF CONTENTS

I. SUMMARY **5**

II. ZUSAMMENFASSUNG **6**

III. ABBREVIATIONS **7**

1. BACKGROUND AND AIMS **10**

1.1 BORDERLINE PERSONALITY DISORDER 10

1.2 EMOTION DYSREGULATION IN BORDERLINE PERSONALITY DISORDER 11

1.2.1 Components of emotion dysregulation 11

1.2.2 Self-concept and emotion dysregulation 12

1.2.3 Deficits in self-awareness and self-regulation 12

1.2.4 Neural correlates of emotion dysregulation 13

1.3. RELEVANCE OF NEUROBIOLOGY FOR TREATMENT IN BPD 15

1.4. AIMS 16

1.4.1 Scientific outline 16

1.4.2 Specific aims - Study 1 16

1.4.3 Specific aims - Study 2 17

1.4.4 Specific aims - Study 3 17

2. METHODS **19**

2.1 fMRI 19

2.2 REAL-TIME fMRI NEUROFEEDBACK 19

3. EMPIRICAL PART **21**

3.1 OVERVIEW 21

3.2 STUDY 1 22

3.3 STUDY 2 43

3.3 STUDY 3 63

4. GENERAL DISCUSSION **78**

4.1 SYNOPSIS 78

4.2 MAIN FINDINGS 78

4.3 COMMON GROUND 80

4.4 IMPLICATIONS FOR FUTURE RESEARCH 83

4.5 LIMITATIONS 85

4.5.1 Limitations Study 1 and Study 2 85
4.5.2 Limitations Study 3 85
4.6 CONCLUDING REMARKS 86

5. REFERENCES 87

IV. APPENDIX 103
SUPPLEMENTARY MATERIAL OF STUDY 1 103
SUPPLEMENTARY MATERIAL OF STUDY 2 107
SUPPLEMENTARY MATERIAL OF STUDY 3 111
CURRICULUM VITAE 112

I. SUMMARY

Borderline personality disorder (BPD) is a serious psychiatric illness encompassing a characteristic pattern of dysfunctional emotion regulation, poor impulse control, and disturbed self-related awareness. Over the past years, the neurobiological aspects underlying psychopathological features of BPD have been more increasingly investigated by functional magnetic resonance imaging (fMRI). The main goal of this thesis was, first, to gain more insights into the neural processes implicated in emotion dysregulation in BPD and, second, to obtain a more comprehensive perspective for potential clinical applications. For this purpose, three studies were performed. *Study 1* and *Study 2* emphasized on the basic understanding of dysfunctional emotion processing circuits in patients with BPD in the absence of specific and concrete stimuli. *Study 3* served as a pilot study including a small group of healthy participants, while aiming at developing a tool that enables subjects to improve emotion regulation by means of real-time fMRI neurofeedback. The first two investigations demonstrate that already anticipatory processes as well as pure self-focus mechanisms are altered in BPD on the neural level. Results show that deficiencies in early self-regulation mediated by the prefrontal cortex may contribute to the overall problems in emotion regulation. These difficulties, in fact, could derive from a limited interaction between emotional and cognitive components as well as from altered processing of self-relevant information. Moreover, findings suggest that neurobiological processes between self-related emotions and cognitions are not clearly differentiated in BPD, which might have implications for therapeutic effects by mindfulness training. *Study 1* and *Study 2* further indicate that individuals with BPD may be more prone to dysregulated behaviors as they demonstrated increased activation patterns in brain areas associated with a 'readiness-to-act network'. Findings suggest that the neurofunctional mechanisms underlying poor self-regulation in BPD may benefit from applying a neurobiological approach using real-time fMRI neurofeedback. In this regard, *Study 3* provides promising relevance towards clinical treatment in the emotional context.

II. ZUSAMMENFASSUNG

Die Borderline-Persönlichkeitsstörung (BPS) ist eine schwerwiegende psychiatrische Erkrankung, bei der die Betroffenen unter dysfunktionaler Emotionsregulation, gestörter Impulskontrolle sowie unter beeinträchtigter Selbstwahrnehmung leiden. Die wachsenden Möglichkeiten funktioneller Bildgebungsverfahren (fMRT) in den letzten Jahren ermöglichten es klinischen Neurowissenschaftlern neurobiologische Aspekte hinsichtlich der Psychopathologie zu untersuchen. Hauptziel der vorliegenden Dissertation war es einerseits weitere Erkenntnisse in Bezug auf die neuronalen Mechanismen der beeinträchtigten Emotionsregulation zu gewinnen, sowie auch neue Perspektiven für potentielle klinisch-biologische Interventionen zu finden. Dazu wurden drei Studien durchgeführt. Während *Studie 1* und *Studie 2* sich mit der Untersuchung von grundlegenden dysfunktionalen Verarbeitungsprozessen emotionaler Informationen ohne konkrete Stimuli bei BPS auseinander setzten, fungierte *Studie 3* als eine Pilotstudie mit einer kleinen Gruppe von gesunden Probanden, bei der das Prinzip der Verbesserung der Emotionsregulation durch Echtzeit-Neurofeedback mittels fMRT etabliert und verbessert werden sollte. Die ersten zwei Studien zeigten, dass Defizite in der Emotionsverarbeitung bei BPS bereits während der Erwartung von emotionalen Stimuli vorliegen und dass neuronale Unterschiede zwischen Gesunden und Patienten mit BPS bereits bei einer rein mentalen Auseinandersetzung mit der eigenen Person bestehen. Die Ergebnisse zeigten, dass verminderte präfrontale 'Top-down-Kontrolle', zusätzlich zur eingeschränkten Interaktion zwischen emotionalen und kognitiven Prozessen, während der frühen Selbstregulation Einfluss auf die allgemeinen Schwierigkeiten in der Emotionsregulation in BPS haben könnte. Ergebnisse deuten weiter darauf hin, dass neurobiologische Mechanismen zwischen selbst-referenziellen Emotionen und Kognitionen in BPS nicht eindeutig differenziert sind, was Auswirkungen auf einen Therapieeffekt durch achtsamkeitsbasiertes Training haben könnte. Zudem fanden wir in den ersten beiden Studien Hinweise darauf, dass erhöhte Hirnaktivität in Regionen, die mit Handlungsbereitschaft assoziiert sind, eine wichtige Rolle für typische BPS-Verhaltensstörungen spielen könnte. Darüber hinaus deuten die Ergebnisse darauf hin, dass neurofunktionale Mechanismen, die einer gestörten Selbstregulation in BPS zugrunde liegen, von der Anwendung durch Echtzeit-Neurofeedback mittels fMRT profitieren könnten. *Studie 3* zeigte in dieser Hinsicht Potential für die Anwendbarkeit dieser Methode im emotionalen Kontext.

III. ABBREVIATIONS

ACC	Anterior cingulate cortex
ADHD	Attention deficit disorder
BA	Brodmann area
BCI	Brain computer interfaces
BDI	Beck depression scale
BOLD	Blood oxygenation level dependent
BPD	Borderline personality disorder
BPS	Borderline-Persönlichkeitsstörung
BSL-23	Borderline symptom list
CBF	Cerebral blood flow
CBV	Cerebral blood volume
$CMRO_2$	Cerebral metabolic rate of oxygen
CTQ	Childhood Trauma Questionnaire
dACC	Dorsal anterior cingulate cortex
DBT	Dialectical behavior therapy
DLPFC	Dorsolateral prefrontal cortex
DMPFC	Dorsomedial prefrontal cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4^{th} edition
DSS4-acute	Dissociation tension scale
EEG	Electroencephalography
EPI	Eysenck Personality Inventory
FMI	Freiburg Mindfulness Inventory
fMRI	Functional magnetic resonance imaging
fMRT	Funktionelle Magnetresonanztomographie
GLM	General linear model
HAMD-21	Hamilton Depression Scale

HC	Healthy controls
IAPS	International Affective Pictures System
ICD-10	International Statistical Classification of Diseases and Related Health Problems
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobe
IPS	Inferior parietal sulcus
L	Left
LGN	Lateral general nucleus
MAAS	Mindful Attention and Awareness Scale
MADRS	Montgomery-Asberg Depression Rating Scale
MBCT	Mindfulness-based cognitive therapy
MCC	Middle cingulate cortex
MDD	Major depressive disorder
MINI	Mini Neuropsychiatric Interview
MPFC	Medial prefrontal cortex
OFC	Orbitofrontal cortex
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
PFC	Prefrontal cortex
PPI	Psychophysiological interaction analysis
pre-SMA	Anterior portion of the supplementary motor area
PTSD	Post-traumatic stress disorder
R	Right
RFX	Random effects whole brain group comparison
ROI	Region of interest
S1	Somatosensory cortex

SD	Standard deviation
SDS	Self-rating depression scale
SEM	Standard error of the mean
SMG	Supramarginal gyrus
SNF	Swiss National Science Funds
SPSS	Statistical Package for the Social Sciences
STAI	Spielberger State-Trait Anxiety inventory
STG	Superior temporal gyrus
TBV	TurboBrainvoyager
V1	Primary visual cortex
VLPFC	Ventrolateral prefrontal cortex
VMPFC	Ventromedial prefrontal cortex

1. BACKGROUND AND AIMS

1.1 BORDERLINE PERSONALITY DISORDER

Borderline personality disorder (BPD) is a serious and debilitating psychiatric disorder characterized by a severe dysregulation of the emotional system (Leichsenring et al., 2011; Lieb et al., 2004). The prevalence of BPD is estimated to affect about 3% of the general population (Bohus and Kröger, 2011; Trull et al., 2010). It is the most common personality disorder comprising 10% of all psychiatric outpatients and about 20% of inpatients (Leichsenring et al., 2011). Individuals with the diagnosis of BPD suffer from a wide range of symptoms including dysfunctional emotion regulation, poor impulse control, and distorted self-image (Lieb et al., 2004). Difficulties specifically concerning awareness, attention, and acceptance towards internal and external experiences play a central role in this illness (Cheavens et al., 2005; Linehan, 1993a). According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV (American Psychiatric Association, 2000)), the diagnosis of BPD is indicated by at least five of the nine following criteria:

1) Frantic efforts to avoid real or imagined abandonment.[1]
2) A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
3) Identity disturbance: markedly and persistently unstable self-image or sense of self.
4) Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating).[1]
5) Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior
6) Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7) Chronic feelings of emptiness
8) Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)
9) Transient, stress-related paranoid ideation or severe dissociative symptoms.

[1] Does not include suicidal or self-mutilating behavior covered in Criterion 5

In addition to the above, it is very common that patients with BPD also meet DSM criteria for other psychiatric disorders (Gunderson et al., 2008; Lieb et al., 2004). Among those, Axis I disorders, including major depression, substance abuse, post-traumatic stress disorder, anxiety disorders, and/or eating disorders can often co-occur (e.g. McGlashan et al., 2000). Psychiatric comorbidities, along with the variations in degrees of the main BPD criteria, therefore can lead to a high heterogeneity in BPD patients making it challenging to formulate a clear-cut definition of the disorder. Yet, regardless of the diversity in BPD psychopathology, emotional instability and distinct problems in emotion regulation are frequently characteristic for all patients diagnosed with BPD (Lieb et al., 2004; Linehan, 1993a).

1.2 EMOTION DYSREGULATION IN BORDERLINE PERSONALITY DISORDER

1.2.1 Components of emotion dysregulation

According to Linehan's biosocial theory, emotion dysregulation as a main diagnostic symptom for BPD is influenced by interactions between individual susceptibilities and specific environmental factors. As the wide-ranging dysregulation of affect appears on all levels of emotional responsiveness, individuals with BPD display heightened emotional sensitivity, inability to regulate their strong emotional responses appropriately, and only slowly return back to baseline. Hence, this affective instability potentially results in maladaptive reactions during emotionally provocative events. Generally speaking, increased emotional sensitivity in combination with an impairment to modulate affective responses is highly linked to disturbed emotion processing in BPD (Crowell et al., 2009; Linehan, 1993a).

In extension of the biosocial model, Carpenter and Trull conceptualized that emotion dysregulation in BPD comprises four elements, that is (1) emotion sensitivity, (2) heightened and labile affect, (3) a deficit of appropriate regulation strategies, and (4) an excess of maladaptive regulation strategies (Carpenter and Trull, 2013). This multi-component model of emotion dysregulation takes into account that while individuals with BPD are more responsive to emotional stimuli from birth, their heightened negative affect and emotional instability makes it more difficult to learn and to apply proper regulation strategies, which in turn leads to a higher probability of maladaptive and impulsive reactions, eventually resulting in negative consequences. This again promotes emotional sensitivity continuing with the cycle of emotion dysregulation in the context of negative stimuli (Fig. 1).

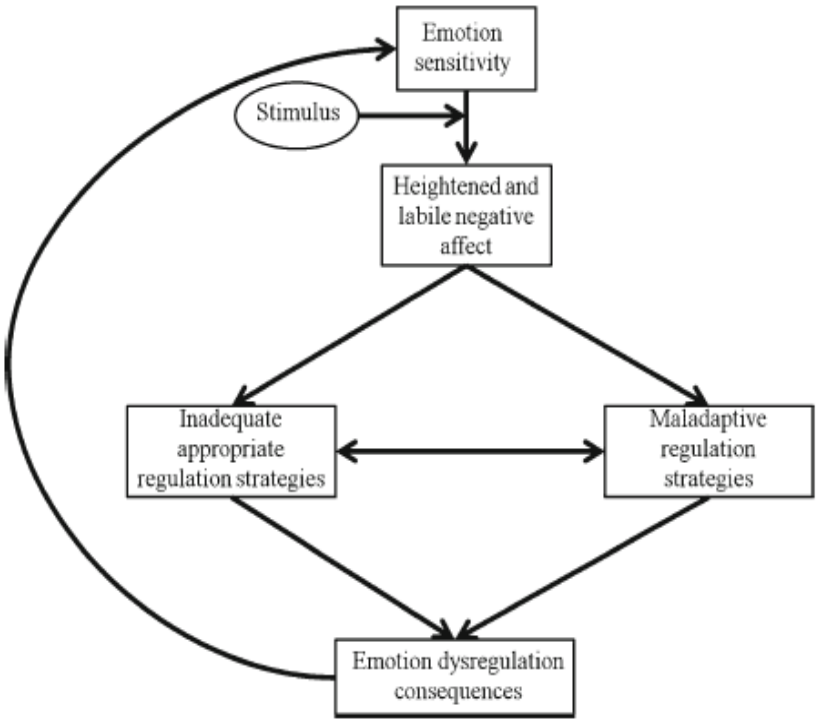

Fig. 1 Multi-component model of emotion dysregulation in BPD

[Figure adapted from Carpenter & Trull (2013); permission obtained from Springer]

1.2.2 Self-concept and emotion dysregulation

A distorted self-concept takes up an important role in the BPD psychopathology. In the literature, the view of identity disturbance in BPD refers to the inability to integrate positive and negative representations of the self, but also of others, which then results in a constantly shifting perspective of the self, e.g. switching between good and bad within minutes (Kernberg, 1975). This unsteadiness of an accurate self-perspective leaves behind the feeling of emptiness, making it difficult for patients with BPD to develop a consistent picture of the self. The lack of a stable self-image and self-awareness can lead to severe functional impairments (Lieb et al., 2004) and maladaptive strategies in regulating negative emotions (Levy et al., 2007). In such cases, patients usually tend to exhibit impulsive and self-destructive behaviors, as for instance self-injury, substance abuse, or suicide attempts (American Psychiatric Association, 2000), when coping with inner distress and uneasiness.

1.2.3 Deficits in self-awareness and self-regulation

Self-regulation, in general, is an essential feature for everyday life situations in dealing with reflexive fear- and/or anger- driven behavior. The awareness for inner feelings and emotions represents a central function within the self-regulation cascade (Churchland, 2002; Damasio et al., 2000). Individuals with BPD typically have problems with experiencing current emotions and uncomfortable situations (Cheavens et al., 2005; Leible and Snell Jr, 2004; Linehan, 1993a),

while they tend to avoid those (Bijttebier and Vertommen, 1999; Chapman et al., 2005). However, once the point is reached where patients no longer are able to avoid severe discomfort, the struggle to suppress the experience turns into fast and thoughtless reactions (Chapman et al., 2005; Kehrer and Linehan, 1996).

In this context, the construct of deficits in mindfulness skills has received more attention in the BPD literature. The term 'mindfulness', in general, describes a mental state in which one is attentive, aware, and accepting of the present moment, without becoming over-involved in cognitive or emotional reactions (Kabat-Zinn, 1982). Through mindful awareness, for instance, one is capable to step back mentally from the automatic urge to respond impulsively towards negative stimuli (Teasdale et al., 2002). Studies on BPD have found support that low abilities in mindfulness may contribute to BPD specific difficulties in emotion regulation (e.g. Fossati et al., 2011; Wupperman et al., 2008; Wupperman et al., 2009). Destructive behaviors that are typically observed in this illness have been associated with the level of mindfulness. In fact, the severity of impulsive reactions, negative affect, anger, and anxiety appears to be closely linked to mindfulness deficits (Brown and Ryan, 2003; Wupperman et al., 2013) and are also likely to play an important role in dysfunctional coping with affective situations adding to the problems with emotion regulation in BPD (e.g. Sanislow et al., 2002).

1.2.4 Neural correlates of emotion dysregulation

Understanding the neurobiological mechanisms of BPD has rapidly grown during the past years. Functional neuroimaging has investigated the neural correlates of the disorder revealing a dysfunctional fronto-limbic network of brain regions that seem to mediate emotional dysregulation in BPD (e.g., Krause-Utz et al., 2014; O'Neill and Frodl, 2012; Rosenthal et al., 2008). A disturbed connection between bottom-up emotional reactivity and cognitive top-down control (Cullen et al., 2011; New et al., 2007) has found support in a model of a reduced medial prefrontal modulation of limbic structures in BPD (reviews: Bohus et al., 2004; Mauchnik and Schmahl, 2010; New et al., 2012).

Many fMRI studies on BPD have especially focused on emotion processing brain regions, such as the amygdala during the confrontation with unpleasant stimuli. The amygdala is an important structure for processing emotionally significant events (Ochsner and Gross, 2007; Sergerie et al., 2008). Studying activations in this brain region is therefore of high clinical relevance for BPD. Although most studies on BPD have mainly demonstrated hyper-reactivity of the amygdala when facing patients with different types of stimuli (i.e., aversive pictures: Hazlett et al., 2012; Herpertz et al., 2001; Koenigsberg et al., 2009b; Schulze et al., 2011, faces: Donegan et al., 2003; Minzenberg et al., 2007, or scripts: Driessen et al., 2004), there is also evidence of an opposite

effect in this structure. A recent meta-analysis (Ruocco et al., 2013) found decreased amygdala activations when processing negative emotions compared to neutral conditions in patients with BPD compared to healthy controls. These inconsistent results on amygdala reactivity could be explained, on the one hand, by differences in task methodology and stimulus specificity, but also they might be due to sample characteristics.

In addition to the centrality of dysfunctional limbic processes in BPD, a number of studies have consistently taken into account the role of prefrontal brain areas demonstrating a failure of 'top-down' frontal modulation (review: Krause-Utz et al., 2014). In particular, during emotional provocation, there seems to be a decreased inhibitory effect of control processes mediated by the PFC on hyper-reactive bottom-up emotion generating brain areas (Ruocco et al., 2010; Salavert et al., 2011, review: New et al., 2012). Also findings on alterations in the anterior cingulate cortex (ACC), particularly the more dorsal sub regions (Mauchnik and Schmahl, 2010), have been considered more prominently in the BPD literature. This involves abnormalities in structure (Hazlett et al., 2005; Tebartz van Elst et al., 2003) and in function, where patients mainly showed reduced activations relative to healthy individuals (Donegan et al., 2003; Minzenberg et al., 2007; Schmahl et al., 2003; Schmahl et al., 2004).

Moreover, there are studies that specifically examined deficits in the connectivity within fronto-limbic networks in BPD. For instance, Kamphausen and colleagues, who investigated fear-inducing anticipation, showed that BPD patients compared to healthy participants exhibited increased connectivity of limbic brain structures with ventromedial prefrontal regions, but decreased connectivity of ventral ACC sub regions with the dorsally located parts of the ACC (Kamphausen et al., 2013). The authors concluded that the functional disconnection between ventral and dorsal prefrontal areas may be part of the neural mechanisms underlying emotional dysregulation in BPD patients. Cullen et al. studied overtly and covertly processing of fearful faces and also found connectivity alterations in the cingulate cortex in BPD (Cullen et al., 2011). Their findings revealed a lower connectivity between limbic structures and mid-cingulate cortical regions and higher connectivity between limbic areas and the ventral ACC in BPD patients. Additionally, Koenigsberg and colleagues have examined distancing to negative social cues as a form of emotion regulation and observed less signal change in dorsal subareas of the ACC, further indirectly underpinning a failure of fronto-limbic emotion regulation in BPD (Koenigsberg et al., 2009a). Deficient connectivity between emotion-regulating and emotion-processing brain areas in BPD appear to play a substantive role in the disorder.

1.3. RELEVANCE OF NEUROBIOLOGY FOR TREATMENT IN BPD

Due to the severity of the disorder, the need for treatment in BPD is immense. Several forms of therapeutic interventions are available for patients with BPD. This includes pharmacotherapy, psychotherapy, or the combination of both (Leichsenring et al., 2011). Most psychotherapeutic interventions, e.g. cognitive behavioral therapy (CBT), dialectical behavior therapy (DBT), mindfulness-based cognitive therapy (MBCT), interpersonal and/or psychodynamic treatments (Binks et al., 2006; Zanarini, 2009), aim at reducing intense changes of mood states and emotional reactions. Although psychotherapeutic treatments using mindfulness techniques appear to diminish some clinical symptoms in BPD (meta-analysis: Kliem et al., 2010; Linehan, 1993a; Linehan et al., 2006), there is no clear evidence of the ideal therapy that leads to a remission of BPD diagnostic criteria. On the basis of the complexity of the disorder encompassing the diverse variations in comorbidities and symptoms, it is yet difficult to propose which psychotherapy approach might be most effective (Leichsenring et al., 2011). More individualized methods are therefore necessary to optimize treatment efficacy.

On the neurobiological level, therapy outcome ideally would reflect a reduced and "normalized" activity of for instance the amygdala structure (Schnell and Herpertz, 2007, reviews in general: Beauregard, 2007; Delaveau et al., 2011; DeRubeis et al., 2008; Frewen et al., 2008) and a strengthening of the regulatory system. This being noted, more knowledge is needed about the modulation and interaction mechanisms on emotion processing regions and how these might be affected by therapeutic interventions. Shedding more light onto the neurobiological underpinnings of the illness and identifying target brain areas for specific therapeutic interventions therefore is of high importance. Although BPD has gained increasing interest by clinical neuroscientists over the past years, more progress is needed in terms of an integrative understanding of the emotion processing circuits as well as of disorder specific correlates as targets for biological treatments. Functional magnetic resonance imaging (fMRI) has become influential in distinguishing neural differences between patients with BPD and healthy individuals and how these might be correlated with psychopathological features (review: Krause-Utz et al., 2014). Even so, in order to establish a selective neuropsychotherapy approach (Grawe, 2004), further insights are necessary about specific changes in brain areas underlying altered emotion regulation in BPD.

1.4. AIMS

1.4.1 Scientific outline

In the current thesis, the main goal was, firstly, to better understand neurobiological processes implicated in emotion dysregulation in BPD and, secondly, to obtain a more comprehensive outlook for potential clinical applications. For this purpose, we investigated basic emotion processing mechanisms as early as during the anticipation of emotional stimuli in patients with BPD relative to healthy individuals (*Study 1*). Furthermore, we examined the neural correlates of introspecting on one's own present feelings, which is comparable to a basic mindfulness intervention, and cognitive self-reflection in BPD patients compared to controls and how these processes might be relevant for clinical applications using mindfulness techniques (*Study 2*). In parallel to the above, we aimed at developing a tool targeting the disturbances in the emotion processing circuitry by training emotion regulation with real-time fMRI neurofeedback (*Study 3*).

1.4.2 Specific aims - Study 1

Most imaging studies on BPD have mainly focused on altered perception of emotional stimuli. However, already the anticipation period prior to actual stimulus exposure can trigger emotional reactions comparable to the actual perception or confrontation (Bermpohl et al., 2006). Biased and dysfunctional anticipatory cognitive-emotional processes may play an important role in the psychopathology of BPD. In this regard, maladaptive cognitions and emotions already during anticipation may affect the perception of the emotional stimulus itself leading to a poor impulse control (Lieb et al., 2004). Enhanced affective responses and emotion dysregulation during the anticipation in BPD might contribute to the typically stronger emotional reactions. Understanding the neural correlates of these anticipatory processes may add valuable insights into the neurobiological mechanisms of emotion dysregulation in this disorder. *Study 1* addressed the neurobiology associated with the anticipation of non-specific, general emotional stimuli of known valence (positive, negative, or neutral) and ambiguous valence (positive or negative). These preparatory mechanisms were analyzed separately in patients with BPD and then compared with healthy participants.

1.4.3 Specific aims - Study 2

Disturbed self-related awareness plays a central role in BPD (Cheavens et al., 2005; Linehan, 1993a; Linehan, 1993b). Psychotherapeutic interventions using mindfulness techniques appear to show effectiveness in reducing clinical symptoms (meta-analysis: Kliem et al., 2010; Linehan, 1993a; Linehan et al., 2006) and represent an alternative regulation strategy for BPD patients in dealing with daily stressors. Although short-term effects of mindful self-focus attention have been reported in BPD (Sauer and Baer, 2012), little is known about its underlying neurobiology and the self-relevant mechanisms behind it. In *Study 2* we investigated the neural mechanisms of self-related emotions and cognitions in BPD patients and their effects on the ability of mindful awareness. We applied a previously well-developed task by our group (Herwig et al., 2010b) addressing the internal self-referential processes. During fMRI scanning participants either performed introspection for one's own present feelings, in the context of a short mindfulness intervention, or cognitive self-reflection. Brain activations were compared between patients with BPD and healthy controls.

1.4.4 Specific aims - Study 3

Dysfunctional emotion regulation in BPD is identified to mainly encompass hyper-arousal and hyper-reactivity along with deficits to modulate emotional responses appropriately (Lieb et al., 2004; Linehan, 1993a). At the neurobiological level, this emotional hyper-reactivity is reflected by increased brain activity in regions involved in the processing of negative emotions, such as the amygdala (e.g., Donegan et al., 2003; Hazlett et al., 2012; Herpertz et al., 2001; Koenigsberg et al., 2009b; Minzenberg et al., 2007; Schulze et al., 2011), and by decreased activations in prefrontal brain areas associated with inhibited top-down control (e.g. Ruocco et al., 2010; Salavert et al., 2011, review: New et al., 2012). Most therapeutic interventions intend to improve emotion regulation and reduce emotional reactions.

Nearly all models of emotion regulation in healthy individuals as well as in other affective disorders propose a top-down effect of emotion regulation strategies modulated by prefrontal regions such as the medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC) and orbitofrontal cortex (OFC), resulting in a decrease of bottom-up emotion propagating brain regions as the amygdala (e.g. Brühl et al., 2008; Herwig et al., 2007b; Ochsner et al., 2002; Ochsner and Gross, 2007; Ochsner et al., 2012; Phan et al., 2005; Schaefer et al., 2002). Typically, most therapeutic approaches including pharmacology and/or psychotherapy interventions therefore aim at diminishing activity and reactivity of emotion processing brain regions. Nevertheless, a substantial amount of patients do not respond to any treatment pointing to the need of refining therapeutic methods. Real-time fMRI could provide a

tool for individualized training by giving direct feedback on the usefulness of an applied regulation intervention. In *Study 3*, we were aiming at developing a method to train subjects to improve control over their own amygdala by providing direct online-feedback when being stimulated by the presentation of negative emotional stimuli. Our goal was to first establish and validate the effectiveness of training self-control of amygdala activity in healthy subjects with the prospective to apply it in patients suffering from affective disturbances, especially in patients with BPD. This might provide a new therapeutic approach combining clinical and neuroscience knowledge.

2. METHODS

2.1 fMRI

Functional magnetic resonance imaging (fMRI) is a commonly used method to investigate brain function (Logothetis et al., 2001). During task-based fMRI, a subject performs a series of mental/motor tasks, while task-related patterns of neural activations can be mapped in his/her brain. Notably, the fMRI technique does not assess neural activity directly, instead it produces a blood oxygenation level dependent (BOLD) response, which is sensitive to the concentration changes of deoxygenated hemoglobin (Ogawa et al., 1990). Hemoglobin is a molecule that has different magnetic properties based on the concentration of O_2. If the molecule is saturated with oxygen (oxyhemoglobin), it takes up diamagnetic properties, however, if some oxygen atoms have been shifted away (deoxyhemoglobin), it transforms into a paramagnetic element. The ratio between deoxyhemoglobin and oxyhemoglobin indicates how the MR signal will be represented in a BOLD image, whereby higher concentration of oxyhemoglobin results in a higher signal and therefore in a brighter point/voxel in the image (Amaro and Barker, 2006). Deoxygenation of hemoglobin, on the other side, is influenced by alterations in cerebral blood flow (CBF), cerebral blood volume (CBV), and cerebral metabolic rate of oxygen ($CMRO_2$) (Uludag et al., 2005). In a typical fMRI experiment using visual stimulation for instance, the presentation of a picture triggers increased neuronal activity in the visual cortex. Subsequently, this leads to increased blood flow, blood volume, and blood oxygen metabolism in the respective brain region. These physiological changes together then result in altered local deoxyhemoglobin having an effect on the MR signal. Temporal properties of a classic BOLD response include a delay of 1 to 2 seconds reaching a maximum after about 8 seconds (varying between 5 and 10 seconds). A post-stimulus undershoot after stimulation is typically observed and usually lasts 15-20 seconds (Uludag et al., 2005).

2.2 REAL-TIME fMRI NEUROFEEDBACK

The bases for real-time fMRI neurofeedback originate from various types of brain computer interfaces (BCI) (e.g. Birbaumer et al., 1999; Nicolelis, 2003; Wolpaw et al., 2002). BCI, so far, has provided a useful method enabling subjects to learn self-regulation of local brain activity. Numerous studies have shown that controlling brain activations can indeed have an effect on behavior and is highly relevant for therapeutic interventions (e.g. Birbaumer and Cohen, 2007; Birbaumer and Kimmel, 1979; Stoyva and Barber, 1971). The concept of neurofeedback as a

strategy to influence mental processes has been especially widely used by Electroencephalography (EEG). Hereby, individuals trained to influence the amplitude or topography of components of EEG-signals (Birbaumer et al., 2006). While EEG-signals, however, rather have a low spatial specificity and a poor signal-to-noise ratio, it is best suited for cortical brain activities. The investigation of activation maps underlying specific mental states and/or psychiatric symptoms, on the other hand, requires higher spatial resolution and a possibility of measuring signal profiles of subcortical structures. Functional MRI properties provide this access and therefore has led to the development of fMRI-based neurofeedback (deCharms, 2007; Weiskopf et al., 2004a). During an fMRI-based neurofeedback experiment, subjects can learn to regulate brain activity with a high spatial specificity by getting feedback on the activity of the selected brain structure. At the same time, real-time fMRI has the advantage to allow online data analysis during image acquisition (Bagarinao et al., 2006). In this way, desired information from acquired fMR images is accessible, while the subject is training self-control of the target region.

A setup for a real-time fMRI neurofeedback normally contains three key components comprising signal acquisition, online analysis, and feedback that are carried out by separate computers (review: Caria et al., 2012). Local brain activity of the selected region is measured with fMRI using the BOLD effect acquired with fast echo planar imaging parameters. This hemodynamic response from neural activity is measured with a delay of about 3-6 seconds (Weiskopf et al., 2007). The data is then retrieved by the online analysis software. Following data preprocessing and statistical analyses, signal time series of the circumscribed region of interest are exported to the software providing feedback to the participant. The presentation of feedback type can vary across different modalities with a delay of a few seconds depending on the paradigm and processing speed (Weiskopf et al., 2007).

3. EMPIRICAL PART

3.1 OVERVIEW

Study 1:

Scherpiet, S., Brühl, A.B., Opialla, S., Roth, L., Jäncke, L., Herwig, U*.: "Altered emotion processing circuits during the anticipation of emotional stimuli in women with borderline personality disorder."* Eur Arch Psychiatry Clin Neurosci. 2014 Feb; 264(1):45-60

Study 2:

Scherpiet, S., Herwig, U., Opialla, S., Scheerer, H., Habermeyer, V., Jäncke, L., Brühl, A.B.: *"Reduced neural differentiation between self-related cognitive and emotional processes in women with borderline personality disorder."* Submitted to Psychiatry Research: Neuroimaging

Study 3:

Brühl, A.B, **Scherpiet, S.**, Sulzer, J., Stämpfli, P., Seifritz, E., Herwig, U.: *" Real-time neurofeedback using functional MRI could improve down-regulation of amygdala activity during emotional stimulation: a proof-of-concept-study."* Brain Topogr. 2014 Jan; 27(1):138-48

3.2 STUDY 1

Altered emotion processing circuits during the anticipation of emotional stimuli in women with borderline personality disorder

Published in European Archives of Psychiatry and Clinical Neuroscience 2014 Feb; 264(1):45-60

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Key words: borderline personality disorder, anticipation, emotion, neurobiology, fMRI

Abstract

Borderline personality disorder (BPD) is associated with disturbed emotion processing, typically encompassing intense and fast emotional reactions toward affective stimuli. In this study we were interested in whether emotional dysregulation in BPD occurs not only during the perception of emotional stimuli, but also during the anticipation of upcoming emotional pictures in the absence of concrete stimuli. 18 female patients with a diagnosis of BPD and 18 healthy control subjects anticipated cued visual stimuli with prior known emotional valence or prior unknown emotional content during functional magnetic resonance imaging (fMRI). Brain activity during the anticipation of emotional stimuli was compared between both groups. When anticipating negative pictures, BPD patients demonstrated less signal change in the left dorsal anterior cingulate (dACC) and left middle cingulate cortex (MCC), and enhanced activations in the left pregenual ACC, left posterior cingulate cortex (PCC) as well as in left visual cortical areas including the lingual gyrus. During the anticipation of ambiguously announced stimuli, brain activity in BPD was also reduced in the left MCC extending into the medial and bilateral dorsolateral prefrontal cortex (MPFC/DLPFC). Results point out that deficient recruitment of brain areas related to cognitive-emotional interaction already during the anticipation phase may add to emotional dysregulation in BPD. Stronger activation of the PCC could correspond to an increased autobiographical reference in BPD. Moreover, increased preparatory visual activity during negative anticipation may contribute to a hyper-sensitivity towards emotional cues in this disorder.

1. Introduction

Borderline personality disorder (BPD) is a serious and debilitating psychiatric disorder with a lifetime prevalence of about 3% (Bohus and Kröger, 2011). It is characterized by a broad constellation of symptoms including affective dysregulation, impaired impulse control, unstable self-image, and problems with cognitive control functions (Leichsenring et al., 2011; Lieb et al., 2004). Regardless of the variety in BPD psychopathology, increased emotional sensitivity in combination with an impairment to modulate emotional responses is highly linked to disturbed emotion processing in this illness (Linehan, 1993b; reviews: Mauchnik and Schmahl, 2010; Rosenthal et al., 2008). Most functional magnetic resonance imaging (fMRI) studies addressing the neurobiology of dysfunctional emotion regulation in BPD patients have focused on emotion processing brain regions, such as the amygdala (review: O'Neill and Frodl, 2012). Nearly all of these studies investigated neural differences during the confrontation with unpleasant stimuli. Irrespective of the stimulus type used, i.e. aversive pictures (Hazlett et al., 2012; Herpertz et al., 2001; Koenigsberg et al., 2009b; Schulze et al., 2011), faces (Donegan et al., 2003; Minzenberg et al., 2007) or scripts (Driessen et al., 2004), a hyper-reactivity of the amygdala and a hypoactivity in prefrontal regions are the most consistent findings in BPD. There is substantial evidence for a disturbed connection between bottom-up emotional reactivity and cognitive top-down control in BPD (Cullen et al., 2011; New et al., 2007) supporting the model of a reduced medial prefrontal modulation of limbic structures (reviews: Bohus et al., 2004; Mauchnik and Schmahl, 2010; New et al., 2012). Lately, findings on alterations in the anterior cingulate cortex (ACC),particularly the more dorsal subregions (Mauchnik and Schmahl, 2010), have become more prominent in the BPD literature. This involves abnormalities in structure (Hazlett et al., 2005; Tebartz van Elst et al., 2003) and in function, where patients predominantly exhibited reduced activations relative to healthy individuals (Donegan et al., 2003; Minzenberg et al., 2007; Schmahl et al., 2003; Schmahl et al., 2004). Hence, this diminished ACC activity in BPD could possibly represent a correlate of disturbed emotion-cognition interaction (Carter, 2000; Ochsner and Gross, 2005), which is a relevant clinical feature of the disorder.

Up to now, imaging studies on BPD have mainly concentrated on altered perception of emotional stimuli. However, already the anticipation period prior actual stimulus exposure is associated with intense emotional processes and is sensitive to distortions and biases on the behavioral level as well as on the neural level (healthy subjects: Herwig et al., 2007a; Herwig et al., 2007c; major depression: Abler et al., 2007; Beck, 1967; Herwig et al., 2010a; anxiety: Bogels and Mansell, 2004; Bruehl et al., 2013; Brühl et al., 2011; Heinrichs and Hofmann, 2001; rodent model: Enkel et al., 2010). Typically, this anticipation phase is characterized by emotional reactions comparable to the actual perception or confrontation Bermpohl et al., 2006) and is

linked to distinct brain areas as the ACC, medial and dorsolateral prefrontal regions (MPFC, DLPFC), amygdala, and others (e.g. Nitschke et al., 2006; Ueda et al., 2003; Wager et al., 2004). Overall, anticipatory processes are eminent cognitive functions. During anticipation, behavioral strategies are developed and decisions for certain actions are made in order to adapt in a changing and potentially arousing environment (Gilbert and Wilson, 2007; Schacter et al., 2007). Biased and dysfunctional anticipatory cognitive-emotional processes may play an important role in the psychopathology of BPD. In particular, BPD patients characteristically have an increased emotional arousal in general. Usually, they show a range of dysphoric affects that go in hand with more rapid and stronger mood reactions combined with poor impulse control (Lieb et al., 2004). These maladaptive cognitions and emotions already during anticipation may affect the perception of the emotional stimulus itself. Enhanced affective responses and emotional dysregulation during the anticipation period in BPD might add to the stronger emotional reactions.

Understanding the neural correlates of these anticipatory processes may add valuable insights into the neurobiological mechanisms of emotional dysregulation in this disorder. To date, neurobiological facets of anticipation in BPD have only been addressed to limited extent. Enzi et al. (Enzi et al., 2013) have recently investigated anticipation in the frame of reward which, however, represents a different construct compared to the anticipation of negative and positive emotional stimuli (Baumeister et al., 2007). On the other hand, Kamphausen and colleagues (Kamphausen et al., 2013), have used an instructed fear task in BPD. Although this is one way to induce anticipatory anxiety (Kalisch et al., 2006), the authors focused on the specific mechanisms underlying social fear learning rather than emotional anticipation in general. Therefore, this fMRI study addressed the neural correlates involved in the anticipation of non-specific, general emotional stimuli of prior known valence (positive, negative, neutral) and prior ambiguous valence (positive or negative) to extend prior fMRI findings in BPD research. Preparatory mechanism during emotional anticipation were analyzed separately in patients with BPD and then compared with healthy participants. Based on the clinical symptoms in BPD patients, we hypothesized that the biased and typically maladaptive cognitive processes would have an effect on anticipation processes prior stimulus exposure already. Hence, we expected to find group differences in brain regions underlying the interaction between cognitive and emotional processes during the anticipation of emotional stimuli, particularly of negative and unknown valence. The main neural correlates assumed to be involved in the emotional-cognitive interplay include cognitive and monitoring regions such as the anterior and middle cingulate cortex (ACC, MCC), MPFC and DLPFC (Koenigsberg et al., 2009a; Olsson and Ochsner, 2008; Vogt et al., 2003; Vogt and Vogt, 2003). Due to the known general intensified emotion processing and dysfunctional emotion regulation circuits in BPD, we expected patients to exhibit a rather lower

engagement in brain regions involved in cognitive and emotional control. Also we expected an increased emotional involvement in BPD reflected in a hyper-reactivity of the amygdala during the anticipation phase.

2. Methods

2.1 Subjects

A total of 22 female BPD patients was recruited from in- and out- patient clinics at the Zurich University Hospital for Psychiatry, Switzerland, and via mailing lists. Four of these patients had to be excluded. One patient aborted the experiment during scan acquisition, another patient had to be excluded due to severe movement artifacts in fMRI images, and two further data sets could not be used due to data loss associated with technical problems of the MRI scanner. The remaining 18 patients were matched by age with a control group of 18 healthy female volunteers. All healthy subjects (HC) were free from psychiatric medication. The two groups did not differ in age (ages 19-50, BPD M_{age} = 28.44, SD = 8.50; HC M_{age} = 28.89, SD = 7.11; t(34) = -.17, p = .87). All subjects were right-handed according to the handedness questionnaire (Annett, 1970). BPD diagnosis was made by the referring physicians of the individual patients using an extensive assessment, which also comprised background and previous psychiatric records. A trained psychiatrist (ABB) and a psychologist (SO) then confirmed the diagnosis of borderline personality disorder according to ICD-10 and DSM-IV criteria (American Psychiatric Association, 2000). To determine the current degree of clinical symptoms, BPD patients completed a short version of the Borderline Symptom List (BSL-23: Bohus et al., 2009; German version: Wolf et al., 2009b), a self-rating questionnaire assessing state borderline-typical symptomatology. Comorbid Axis-I diagnoses were evaluated using the German version (Ackenheil et al., 1999) of the Mini-International Neuropsychiatric Interview for DSM-IV (Sheehan et al., 1998). Patients were excluded if they met DSM-IV criteria for present or previous bipolar I disorder, schizophrenia, or schizoaffective disorder. Due to the known high rate of comorbid psychiatric disorders in BPD (Becker et al., 2000; Lieb et al., 2004), we did not exclude current depressive episodes (Gunderson et al., 2008). We allowed occasional use of cannabinoids and alcohol (Zanarini et al., 2011), but excluded abuse of opioids and benzodiazepines and other psychotropic drugs. Sporadic low dose use of prescribed tranquilizers was allowed (< 3 mg Lorazepam or equivalents per week), though patients were asked to abstain from intake at least 24 hours prior scanning. Among the BPD group eleven subjects took psychotropic medication regularly (ten patients took antidepressants, five patients took mood stabilizers, seven patients took tranquilizers (intermittently), and one patient took low-dose antipsychotic medication). In

all patients the dose of drugs had been qualitatively and quantitatively stable for more than one month according to documentation at the time of participation. No active substance or alcohol consummation at the time of study was reported. Table 1 lists psychotropic medication as well as comorbid lifetime diagnoses of psychiatric disorders for the patient group. A positive family history of psychiatric disorders was present in 55.6% of the patients (mostly depression and alcohol dependence). To assess the level of depression in the patient sample, we obtained ratings on the Hamilton Depression Rating Scale (HAMD: Hamilton, 1960), Montgomery-Asberg Depression Rating Scale (MADRS: Montgomery and Asberg, 1979) and on the Beck`s Depression Inventory (BDI: Hautzinger et al., 1995).

For all participants general exclusion criteria, such as previous or current neurological disorders, head trauma, pregnancy, excessive consumption of alcohol (regular intake of > 7 units/week), and MRI contraindications were assessed during a semi-structured interview prior to scanning. All subjects provided written informed consent after receiving a complete description of the study and were compensated for their participation. The study was approved by the local ethics committee.

Table 1 Comorbid psychiatric disorders and psychotropic medication of the included BPD sample

BPD[a] subjects	Current diagnoses	Lifetime diagnoses	Psychotropic medication
1	–	–	Lamotrigine, escitalopram, quetiapine
2	Substance abuse[b]	MDD[c], ADHD[d]	–
3	Substance abuse	–	Amisulpride, lorazepam[f]
4	Substance abuse, eating disorder	–	–
5	Substance abuse, eating disorder	–	Quetiapine, lamotrigine, venlafaxine
6	Substance abuse	–	Trimipramin, fluoxetine, gabapentin, venlafaxine
7	Substance abuse	–	–
8	–	–	Fluoxetine, quetiapine
9	–	–	–
10	MDD	PTSD[e]	Escitalopram, quetiapine
11	Substance abuse	MDD	Duloxetine, lamotrigin, doxepine
12	–	MDD	–
13	–	PTSD	–
14	–		–
15	ADHD, anxiety disorder	–	Methylphenidate, lamotrigine, mirtazapine, zolpidem
16	MDD	Eating disorder	Escitalopram
17	–	MDD	Citalopram
18	–	–	Sertraline, quetiapine

[a] *BPD* borderline personality disorder
[b] Substance abuse includes alcohol, sedatives, and cannabinoids
[c] *MDD*:major depressive disorder
[d] *ADHD* attention deficit hyperactivity disorder
[e] *PTSD* posttraumatic stress disorder
[f] Given only on a provisional basis, no intake >48 h before scanning

2.2 Self-report measurements

Both groups completed German versions of questionnaires to examine the degree of depression (Self-Rating Depression Scale, SDS: Zung, 2005) and anxiety (State-Trait Anxiety-Inventory, STAI: Laux et al., 1981). Borderline patients additionally completed a retrospective self-report on traumatic childhood experiences (Childhood Trauma Questionnaire, CTQ: Bernstein and Fink,

1998). Due to the known tendency to experience dissociative symptoms, BPD patients were given the DSS-4 acute questionnaire directly after the fMRI experiment to measure their current dissociative state (short version of Dissociation Tension Scale acute, DSS-4: Stiglmayr et al., 2009; Stiglmayr et al., 2003).

2.3 Stimuli

Pictures serving as visual stimuli in this study were taken from the International Affective Picture System (IAPS; Peter Lang, Miami, USA, Lang, 2005). A series of 56 digital color photographs was matched for valence difference (neutral, negative, and positive) according to the IAPS picture ratings as well as for complexity, contents, and, as far as possible, for arousal (for discussion of arousal matching refer to Herwig et al., 2007c). Pictures were presented in a pseudo-randomized order once per experiment. All participants viewed the same stimulus sequence. After scanning, participants were given printouts to rate the emotional valence of the shown pictures on a nine-point Likert scale (1 - very negative, 9 - very positive).

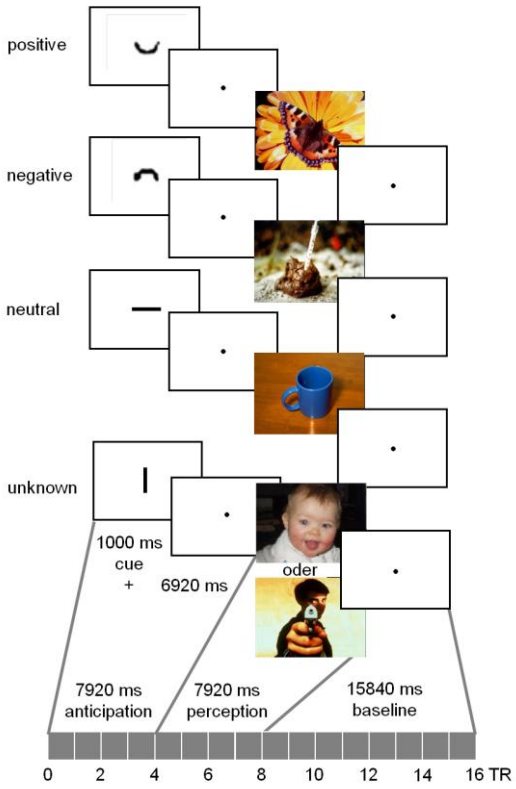

Fig. 1 Illustration of experimental task. Cues are enlarged for presentation reasons. Their actual height in the experiment was about 1/40 screen

2.4 Experimental Paradigm

During fMRI scanning, subjects performed an emotional anticipation task, which allows investigating the anticipation phase and perception phase separately (for reference see Herwig et al., 2007c, Fig1). The participants anticipated and perceived cued emotional pictures of known or unknown valence. In known trials, a cue indicated either a positive "∪", a negative "∩", or a neutral "–" picture after an anticipation period (cue: 1000 ms, anticipation period: 6920 ms). In unknown or ambiguous trials, the symbol "|" indicated an emotional picture of either pleasant or unpleasant content (50% probability each). Following the symbol, a blank black screen with a small white fixation point appeared for 6920 ms (cue + anticipation: four times of MR volume repetition time (TR) 1980 ms = 7920 ms). Subsequently, the respective emotional picture was presented for 7920 ms (4 TR). A baseline period of 15840 ms (8 TR) allowed the BOLD signal to wear off before the next trial. The experimental task consisted of one run including 56

randomized trials, 14 for each condition: known positive (ps), known negative (ng), known neutral (nt) and unknown (uk), with a total duration of 30 min. To familiarize the participants with the task, a practice session was performed outside the scanner prior to the fMRI experiment, showing pictures that were not used in the experiment itself. The paradigm was programmed with Presentation™ (Neurobehavioral Systems, USA) and presented via digital video goggles (Resonance Technologies, Northridge, CA). The cues were intuitive and did not require intensive cognitive resources to understand their meaning. All subjects confirmed that they were able to perform the general task.

2.5 fMRI Data Acquisition

The experiment was performed using a 3.0 T GE Signa™ HD Scanner (GE Medical Systems, Milwaukee, USA) equipped with an eight channel head coil. Echo-planar imaging was performed for fMRI (TR/TE 1980/32 ms, 22 sequential axial slices, whole brain, patient group and 14 subjects of the control group: slice thickness 3.5 mm, 1 mm gap, resulting voxel size 3.125×3.125×4.5 mm, matrix 64×64, FOV 200 mm, flip angle 70°; due to technical reasons changed parameters in 5 subjects of the control group: slice thickness 5 mm, 0.5 mm gap, voxel size 3.4 × 3.4 × 5 mm, FOV 220 mm, flip angle 70°). 908 volumes were obtained per subject. High-resolution 3D T1 weighted anatomical volumes were acquired (TR/TE 9.9/2.9 ms; matrix size 256×256; 1×1×1 mm^3 resolution, axial orientation) for co-registration with the functional data. Furthermore, T2-weighted images in parallel to the EPI sequence were acquired to exclude possible T2-sensitive brain abnormalities.

2.6 Psychometric Analysis

To test differences in depression (SDS) and anxiety (STAI) between both samples, independent t-tests were performed by using the Statistical Package for the Social Sciences (SPSS) version 20. Also, correlations between borderline symptomatology (BSL-23), self-reported dissociation (DSS-4) and depression scales (HAMD, MADRS, BDI) were calculated. A p-value of $p<.05$, 2-tailed, was considered as significant.

2.7 fMRI Data Analysis

Data were analyzed using BrainVoyager™ QX 2.4.0 (Brain Innovation, Maastricht, The Netherlands (Goebel et al., 2006). The first four images of each functional scan were discarded to allow for T1* equilibration effects. Preprocessing of the functional scans included motion correction, slice scan time correction, high frequency temporal filtering, and removal of linear trends. Functional images were superimposed on the 2D anatomical images and incorporated into 3D data sets. The individual 3D data sets were then transformed into Talairach and

Tournoux space (Talairach and Tournoux, 1988) resulting in a voxel size of 3 x 3 x 3 mm and then spatially smoothed with an 8-mm Gaussian kernel for following group analyses. Single trials with fMRI signal artifacts of more than threefold mean signal change amplitude with resulting outliers of beta weights (e.g. due to head movements) were eliminated manually. Anticipation conditions (ng, ps, nt, uk) and the respective perception conditions were implemented in the design matrix resulting in eight predictors and the factor group. Anticipation period and picture presentation were modeled as epochs with the standard two-gamma hemodynamic response function (HRF) adapted to the applied period duration provided by Brain Voyager. The fMRI data analysis based on the general linear model (GLM) involved the following steps: Fixed-effects analyses were calculated separately for each subject for the anticipation phase (a), with the contrasts *anticipation negative versus anticipation neutral* (ang > ant), *anticipation unknown versus anticipation neutral* (auk > ant), and *anticipation positive versus anticipation neutral* (aps > ant) as well as for the perception phase (p) contrasts *negative versus neutral* (png > pnt) and *positive versus neutral* (pps > pnt) resulting in summary images. The respective neutral condition was subtracted in order to focus on emotion processing without general effects of the anticipation and perception of stimuli. The summary images were then subjected to second-level analyses, separately for both, BPD patients and healthy subjects. In the next step, a random effects whole brain group comparison (rfx) for the specified contrasts (ang > ant, auk > ant, aps > ant) was performed. We also investigated group effects during the perception period with the defined contrasts (png > pnt, and pps > pnt). Results on differential neural correlates during the perception of emotional stimuli between the two groups are reported in the supplementary material and are not the focus in this present work (Online Resource 1). To correct for multiple comparisons, maps with a voxel-wise threshold of $p < .005$ were submitted to a Monte Carlo simulation (Goebel et al., 2006) for estimating cluster-level false-positive rates, yielding a corrected cluster-level of $p < .05$.

A hypothesis driven region of interest analysis (ROI) within a predefined cubic ROI in the amygdala (edge length 9 mm, 729 mm^3, centre x, y, z = 19/-19, -5, -17) according to the Talairach Client (Lancaster et al., 2000) was carried out for each contrast during anticipation. Further, the activity in the primary visual cortex (edge length 9 mm, 729 mm^3, centre x, y, z = 5/-5, -86, -3;) and in the lateral geniculate nucleus (LGN) bilaterally (edge length 6 mm, 216mm^3, LGN left: centre x, y, z = -21, -23,-4, LGN right: centre x, y, z = 22, -22, -4; for details on LGN coordinates refer to (Kastner et al., 2004) during the anticipation and perception period was examined to control for general perceptual and attentional differences between groups, as for instance closed eyes or markedly diverted gaze would have resulted in decreased activity in LGN and V1.

3. Results

3.1 Psychometric Data Results

Details on demographic and psychometric data are summarized in Table 2. The evaluation of psychometric data revealed significant differences between both samples in clinically relevant degrees of depression and anxiety. In general, a relevant number of patients showed symptoms of major depression disorder (MDD) according to the clinical depression scales (HAMD-21 score > 20 in ten patients, BDI score > 20 in ten patients, MADRS score > 20 in nine patients). CTQ scores suggested increased traumatic experiences during childhood, in particular on the emotional level. Nine patients scored higher than '16' on emotional neglect and eight patients rated higher than '16' on the emotional abuse scale indicating severe to extreme traumatic experiences during childhood. According to the BSL-23 questionnaire the patient sample showed moderate borderline symptomatology at the time of the experiment. DSS-4 ratings after the fMRI scan propose some degree of dissociative states in the patient sample, whereby eight patients scored above '2' suggesting relevant elevated dissociative experience during scanning. Our sample of control subjects were healthy according to the standard values for questionnaires regarding depression and anxiety (Tanaka-Matsumi and Kameoka, 1986).

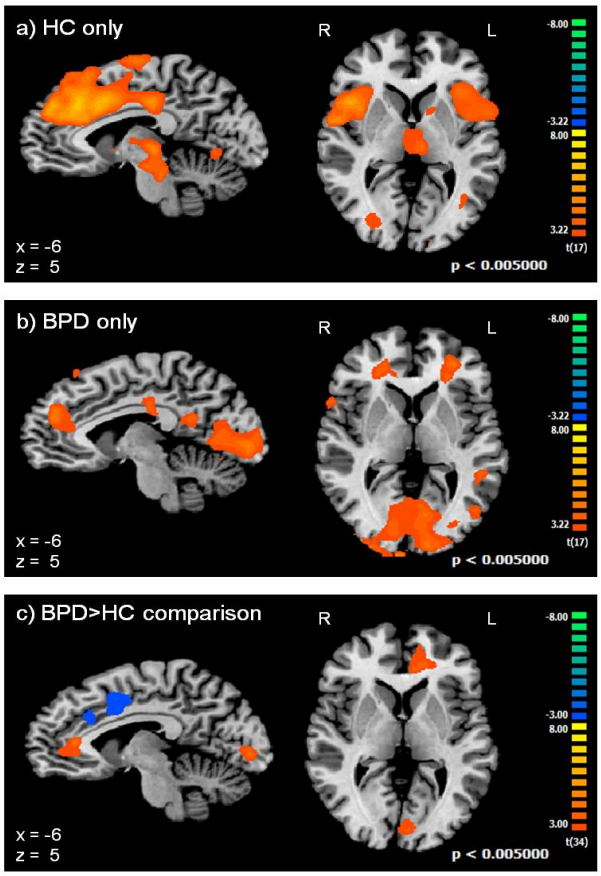

Fig. 2 Contrast anticipation of negative versus anticipation of neutral stimuli (ang>ant) a) in healthy controls only, b) in patients with borderline personality disorder only, and c) in a group comparison BPD>HC. The t values of the contrasts are given in the color bar. *L* left, *R* right, *HC* healthy controls, *BPD* patients with borderline personality disorder

Measurements of depression (HAMD, MADRS, BDI) in the patient sample were highly intercorrelated. Scores of the borderline symptom list and of the dissociation tension scale significantly correlated with all three depression questionnaires. Additionally, we observed a significant positive correlation between BPD symptomatology and self-reported dissociation. (Online Resource 2)

3.2 Behavioral Data Results

The mean ratings of emotional valence for positive (M_{HC} = 7.05, SD_{HC} = 1.29; M_{BPD} = 7.09, SD_{HC} = .87), negative (M_{HC}=2.83, SD_{HC} = .59; M_{BPD} = 2.97, SD_{HC} = .87) and neutral pictures (M_{HC}=5.09, SD_{HC} = .83; M_{BPD} = 5.02, SD_{HC} = .64) did not differ significantly between the two groups (t_{ps} (33) = .091, p = .928; t_{ng} (33) = .579, *p* = .567; t_{nt} (33) = -.266, p = .792). Internal consistencies for positive (Cronbach's α = .839, N = 33), negative (α = .799, N = 34) and for neutral (α = .809, N = 34) valence revealed good internal reliability.

Table 2 Demographic and psychometric characteristics of included subjects

	BPD[a]		HC[b]		*T*	*p*
Sample, *n*	18		18			
Mean age, years (SD)[c]	28.44 (8.50)		28.89 (7.11)		−0.17	<.870
Mean scale scores (SD)						
SDS[d]	68.40 (8.43)	n = 16	37.35 (9.21)	*n* = 17	10.08	<.001*
STAI[e]-X1	51.41 (11.18)	*n* = 17	34.53 (8.64)	*n* = 17	4.93	<.001*
STAI-X2	57.41 (9.26)	*n* = 17	35.82 (10.48)	*n* = 17	6.36	<.001*
BSL-23[f]	1.83 (1.08)	*n* = 17	–			
BDI[g]	26.93 (9.98)	*n* = 16	–			
HAMD-21[h]	22.20 (8.18)	*n* = 15	–			
MADRS[i]	22.53 (8.99)	*n* = 15	–			
DSS-4[j]	2.32 (1.91)	*n* = 15	–			
CTQ[k]—emotional abuse	15.38 (7.26)	*n* = 16	–			
CTQ—physical abuse	11.75 (5.45)	*n* = 16	–			
CTQ—sexual abuse	4.81 (2.48)	*n* = 16	–			
CTQ—emotional neglect	19.13 (9.42)	*n* = 16	–			

[a] *BPD* patients with borderline personality disorder

[b] *HC* healthy subjects

[c] *SD* standard deviation

[d] *SDS* Self-Rating Depression Scale (score <50: not depressed)

[e] *STAI* Spielberger State-Trait Anxiety Inventory, X1: state section; X2: trait section

[f] *BSL-23* Borderline Symptom List 23 [scores between 0 (= none) and 4 (= very much) represent current borderline symptomatology]

[g] *BDI* Beck Depression Scale (score <15: not depressed)

[h] *HAMD-21* Hamilton Depression Scale (score <15: not depressed)

[i] *MADRS* Montgomery–Asberg Depression Rating Scale (score <20: not depressed)

[j] *DSS-4* short version of Dissociation Tension Scale acute

[k] *CTQ* Childhood Trauma Questionnaire (subscale score <5–8: minimal-to-none traumatic experience, subscale score ≥16: severe-to-extreme traumatic experience)

3.3 fMRI Data Results

3.3.1 Whole-brain analysis in the BPD group during emotional anticipation

When anticipating negative compared to neutral pictures, patients showed increased brain activity in the right ventral anterior cingulate cortex (ACC) including a large cluster of the medial frontal gyrus as part of the medial prefrontal cortex (MPFC), in the right lingual gyrus and cuneus, and in the left posterior cingulate cortex (Fig2). The anticipation of pictures with ambiguous emotional content versus neutral pictures activated the right inferior frontal gyrus within the ventrolateral prefrontal cortex (VLPFC) and the insula in patients with BPD. The contrast anticipation of positive versus neutral stimuli revealed activations in the right lingual

gyrus, left superior occipital gyrus extending into the angular gyrus, and also in the left medial frontal gyrus. Details are given in Table 3.

3.3.2 Whole-brain analysis in the HC group during emotional anticipation

Healthy subjects showed large activation clusters of increased brain activity in the right anterior cingulate cortex (ACC) extending into the midcingulate cortex (MCC) and parts of the medial prefrontal cortex (MPFC) during the anticipation of negative compared to neutral pictures. Enhanced brain activity was also found in the insula bilaterally, in the right middle occipital gyrus, right culmen, and in the left thalamus and midbrain during the respective contrast (Fig2). Anticipating pictures of unknown valence in comparison with the anticipation of neutral pictures revealed increased brain activity covering the bilateral insula, left inferior frontal gyrus, left precentral-, middle-, and superior frontal gyrus within the DLPFC, the left MCC and ACC extending into the medial frontal gyrus, and the inferior parietal lobe (IPL) bilaterally. The right lingual gyrus, however, was less activated during the anticipation of unknown stimuli relative to neutral. When anticipating positive compared to neutral pictures control subjects showed enhanced brain activity in the right precentral gyrus, right medial frontal gyrus, right lingual gyrus and cuneus, and in the left middle temporal gyrus. For details refer to Table 4.

Table 3 Whole-brain activations in the BPD sample during emotional anticipation

Anatomic region	Lat	BA	Cluster size (mm^3)	Peak Talairach coordinates			*t*-max	*p*-max
				x	*y*	*z*		
(a) Anticipation of negative stimuli > anticipation of neutral stimuli								
Lingual gyrus/cuneus	R	18/17	24,853	−11	−102	6	5.0	.000102
Medial frontal gyrus/ACC	R	9/32	14,146	2	43	30	5.7	.000025
Posterior cingulate/caudate tail	L	31	15,945	−16	−35	24	8.0	.000000
(b) Anticipation of unknown stimuli > anticipation of neutral stimuli								
Inferior frontal gyrus/insula	R	47/13	1,287	32	22	−3	4.4	.000419
(c) Anticipation of positive stimuli > anticipation of neutral stimuli								
Lingual gyrus	R	18	4,913	8	−83	0	4.6	.000280
Superior occipital gyrus/angular gyrus	L	39	2,366	−55	−65	21	4.9	.000148
Medial frontal gyrus	L	10	1,664	−13	52	6	4.1	.000740

Activated areas in a random-effects analysis (rfx) in the BPD sample with a voxel-wise threshold of $p < .005$. Activated minimum cluster size for global error probability (Monte Carlo correction) of $p < .05$: (a) anticipation of negative stimuli > anticipation of neutral stimuli. Minimum cluster threshold: 1,383 mm^3 (52 functional voxels), (b) anticipation of unknown stimuli > anticipation of neutral stimuli, cluster-threshold: 840 mm^3 (32 functional voxels), and (c) anticipation of positive stimuli > anticipation of neutral stimuli, cluster-threshold: 1,106 mm^3 (43 functional voxels)

ACC anterior cingulate cortex, *BA* Brodmann area, *Lat* lateralization, *R* right, *L* left

3.3.3 Group comparison (BPD > HC) during emotional anticipation

Whole-brain analyses during the anticipation of negative compared to neutral stimuli revealed reduced brain activity in the left dorsal ACC as well as in the left MCC in patients relative to controls (Fig4). As opposed to healthy participants, the BPD sample additionally showed increased brain activity in the left pregenual ACC, left lingual gyrus, and in the left posterior cingulate cortex (PCC) during the same contrast (Fig3). When anticipating stimuli with unknown valence versus neutral, patients showed reduced brain activations in the left MCC extending into the medial frontal gyrus within the MPFC region (Fig4), in the left precentral gyrus and in the right middle frontal gyrus belonging to the DLPFC. Further, reduced brain response in the left intraparietal sulcus (IPS), right precentral gyrus, and in the right inferior temporal gyrus during the same contrast was found in BPD patients compared to healthy participants. Differential activations between the two groups during the anticipation of positive versus neutral pictures did not survive the Monte Carlo correction for multiple comparisons (for details refer to Table 5).

Table 4 Whole-brain activations in the HC sample during emotional anticipation

Anatomic region	Lat	BA	Cluster size (mm^3)	Peak Talairach coordinates			*t*-max	*p*-max
				x	*y*	*z*		
(a) Anticipation of negative stimuli > anticipation of neutral stimuli								
Dorsal ACC/MCC/MPFC	R	8/9/32	61,388	5	25	27	7.6	.000001
Middle occipital gyrus	R	18	5,004	29	−83	−9	4.9	.000124
Culmen	R		2,276	8	−62	−6	4.4	.000424
Insula	R	13	17,852	41	13	0	6.5	.000005
Insula/superior temporal gyrus	L	13/22	12,608	−52	7	0	6.5	.000005
Thalamus/midbrain	L		6,443	−7	−23	0	5.4	.000044
(b) Anticipation of unknown stimuli > anticipation of neutral stimuli								
Insula/Inferior frontal gyrus	R	13/47	7,088	32	16	0	5.7	.000028
Insula	L	13	5,571	−31	22	3	6.7	.000004
Middle frontal gyrus/DLPFC	L	9	3,254	−40	16	45	5.2	.000064
Precentral/middle/superior frontal gyrus/DLPFC	L	4/6/8/9/44	3,603	−43	−2	54	5.1	.000090
ACC/MCC/medial frontal gyrus	L	6/24/32	48,909	−10	16	36	7.4	.000001
Inferior parietal lobe/supramarginal gyrus	L	40	3,711	−58	−56	33	5.6	.000032
Inferior parietal lobe	R	40	2,719	50	−50	33	4.7	.000216
Lingual gyrus	R		1,533	8	−53	9	−5.8	.000020
(c) Anticipation of positive stimuli > anticipation of neutral stimuli								
Precentral gyrus	R	4	3,365	41	−17	36	5.0	.000119
Medial frontal gyrus	R	6	1,402	8	−8	54	5.0	.000100
Lingual gyrus/cuneus	R	17	7,423	20	−80	9	5.6	.000035
Middle temporal gyrus	L	19	1,092	−31	−56	9	4.8	.000173

Activated areas in a random-effects analysis (rfx) in the HC sample with a voxel-wise threshold of $p < .005$. Activated minimum cluster size for global error probability (Monte Carlo correction) of $p < .05$: (a) Anticipation of negative stimuli > anticipation of neutral stimuli. Minimum cluster threshold: 1,616 mm^3 (59functional voxels), (b) Anticipation of unknown stimuli > anticipation of neutral stimuli, cluster-threshold: 1,502 mm^3 (56 functional voxels), and (c) Anticipation of positive stimuli > anticipation of neutral stimuli, cluster-threshold: 1,032 mm^3 (40 functional voxels)

HC healthy controls, *ACC* anterior cingulate cortex, *MCC* midcingulate cortex, *MPFC* medial prefrontal cortex, *DLPFC* dorsolateral prefrontal cortex, *BA* Brodmann area, *Lat* lateralization, *R* right, *L* left

Table 5 Whole-brain group comparison (BPD > HC) during the anticipation of emotional stimuli

Anatomic region	Lat	BA	Cluster size (mm^3)	Peak Talairach coordinates			*t*-max	*p*-max
				x	*y*	*z*		
(a) Anticipation of negative stimuli > anticipation of neutral stimuli								
MCC	L	24	4,450	−10	4	42	−3.9	.000481
Dorsal ACC	L	32	1,222	−10	22	24	−4.5	.000068
Pregenual ACC	L	32	3,282	−16	37	24	5.2	.000008
Lingual gyrus	L	18	1,131	−4	−86	0	4.5	.000074
Posterior cingulate	L	31	866	−19	−38	24	4.6	.000062
(b) Anticipation of unknown stimuli > anticipation of neutral stimuli								
MCC/medial frontal gyrus	L	24/32/6	5,603	−13	13	36	−5.1	.000015
Precentral gyrus	L	6	920	−61	−5	27	−3.9	.000433
Intraparietal sulcus	L	7	739	−25	−68	36	−3.8	.000666
Middle frontal gyrus/DLPFC	R	9	800	26	28	24	−3.6	.000880
Precentral gyrus	R	4	798	41	−17	48	−3.5	.001182
Inferior temporal gyrus	R	20	837	47	−32	−15	−3.8	.000555
(c) Anticipation of positive stimuli > anticipation of neutral stimuli								
Exploratory results for cluster-threshold: 135 mm^3								
Ventral ACC	R	24	315	8	28	9	3.4	.001921
Ventral ACC	L	24	393	−13	34	9	3.6	.000911
Thalamus	L		235	−4	−5	0	3.7	.000871
Medial frontal gyrus	L	10	289	−13	52	6	3.5	.001341

FMRI analysis of emotion anticipation in the BPD group versus the control group. Activated areas in a random-effects analysis (rfx) with a voxel-wise threshold of $p < .005$ mean that the contrast difference (anticipation of emotional stimuli > anticipation of neutral stimuli) were greater in the BPD group compared to the control group. (a) Anticipation of negative stimuli > anticipation of neutral stimuli. Minimum cluster size for global error probability of $p < .05$: 729 mm^3 (28 functional voxel). (b) Anticipation of unknown stimuli > anticipation of neutral stimuli. Minimum cluster size for global error probability of $p < .05$: 760 mm^3 (29 functional voxel). (c) Minimum cluster size for global error probability (Monte Carlo correction) of $p < .05$: 593 mm^3 (23 functional voxels) showed no differences between the groups during the anticipation of positive stimuli > anticipation of neutral stimuli, but clusters exceed a threshold of 135 mm^3 (5 functional voxels)

ACC anterior cingulate cortex, *MCC* midcingulate cortex, *DLPFC* dorsolateral prefrontal cortex, *BA* Brodmann area, *Lat* lateralization, *R* right, *L* left

There were no significant correlations between clinical symptoms, including scores of the borderline symptom list (BSL) and scores of the dissociation tension scale (DSS4-acute) and the beta weights of the above mentioned significant differential activations in the BPD sample (Online Resource 4).

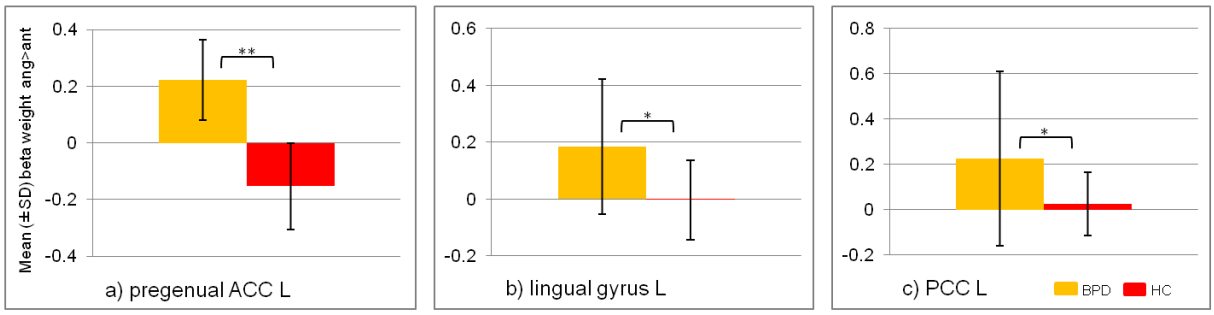

Fig3. Enhanced brain activity in BPD patients compared to healthy controls during the anticipation of negative versus neutral pictures (contrast *ang* > *ant*). Given are the mean beta-weights within a) left pregenual ACC (x = -16, y = 37, z = 24), (t (34) = 3.63, p < .001), b) left lingual gyrus (x = -4, y = -86, z = 0), (t (34) = 2.78, p < .01), and c) left PCC (x = -19, y = -38, z = 24), (t (34) = 3.29, p < .002), as derived from the contrast analyses. Error bars indicate standard deviations. *ACC* anterior cingulate cortex, *PCC* posterior cingulate cortex, *BPD* borderline personality disorder

3.3.4 ROI analyses

ROI analyses in the predefined amygdala region showed no significant group differences, irrespective of contrast. ROI analyses investigating hemodynamic differences in V1 and LGN revealed that BPD patients compared to healthy controls showed increased brain activity in the left primary visual cortex when anticipating negative versus neutral stimuli (t (34) = 2.31, p < .03, Cohen's d = .62, medium effect). The lateral geniculate nucleus (LGN) was bilaterally not differentially activated in any contrast during emotional anticipation between both samples (for details refer to Online Resource 3).

4. Discussion

We investigated the neural correlates of the anticipation of non-specific, general emotional stimuli (negative, positive, and unknown) in relation to neutral pictures in patients with BPD compared to healthy participants. BPD patients showed neural differences in anticipating cued emotional pictures, in particular those of known negative and potentially negative valence, but not of positive stimuli. Differential activations were primarily detected in functional alterations of the cingulate cortex and adjacent prefrontal regions as well as in the visual cortex. Our study provides evidence that disturbed emotion processing in BPD also occurs during the anticipation of emotional stimuli, in addition to disturbances during the actual perception phase (e.g. Donegan et al., 2003; Herpertz et al., 2001; Koenigsberg et al., 2009b; Minzenberg et al., 2007). Reduced brain activity in cognition-related areas and increased activations in the pregenual ACC and in the visual cortex during emotional anticipation in BPD patients indicate a disturbance in cognition-emotion interaction and a heightened visual sensitivity to negative cues. Moreover, enhanced activation in the PCC area suggests an increased autobiographical reference in BPD, even though no specific stimuli were anticipated.

The cognitive domain of emotion regulation comprises particularly the anterior cingulate as well as the medial and dorsolateral prefrontal cortical brain regions (Ochsner et al., 2012). In our study, left dorsal ACC and MCC were less active in patients compared to healthy controls during the anticipation of negative stimuli. During the anticipation of ambiguously cued pictures, patients exhibited additionally reduced activations in the MPFC (adjacent to the MCC) and DLPFC. With regard to the interaction of cognitive and emotional processes, dorsal subregions of the cingulate cortex have been associated with cognitive processes such as attention for action, anticipation, and action selection (Bush et al., 2000; Carter et al., 1998; Murtha et al., 1996; Pardo et al., 1990; Posner et al., 1988; Rushworth et al., 2007; Vogt et al., 2003). Moreover, functions related to integration and control of emotional stimuli (Carter, 2000; Ochsner and

Gross, 2005; Vogt, 2005) as well as the anticipation of unpleasant stimuli (Herwig et al., 2007a) have been linked to the cingulate cortex. In parallel, prefrontal regions including the MPFC and DLPFC play a central role in selecting, implementing, and monitoring cognitive control and executive strategies (Ochsner and Gross, 2005) and in emotion regulation (Diekhof et al., 2011; Disner et al., 2011; Kalisch, 2009; Kanske et al., 2011).

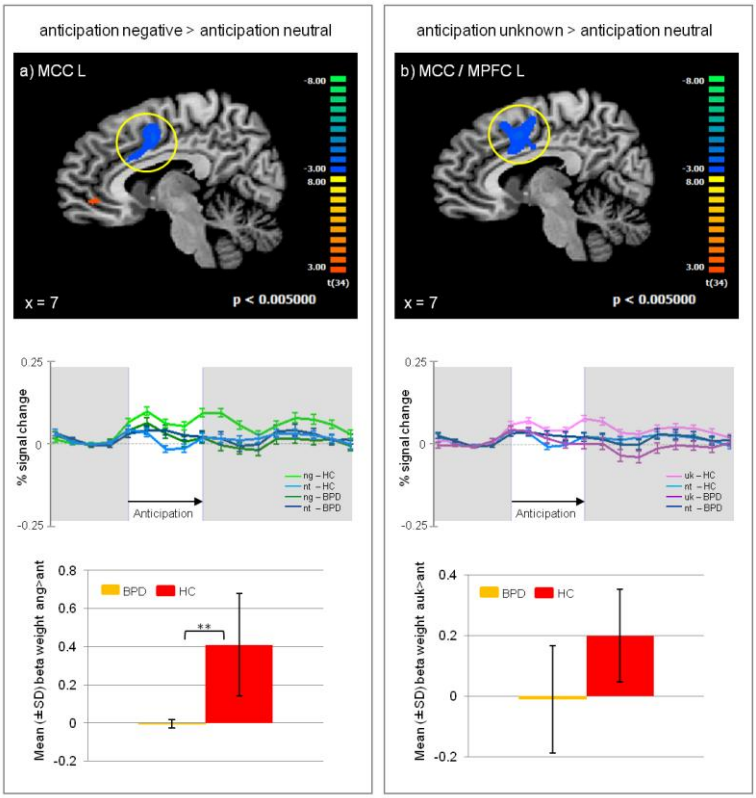

Fig4. Reduced activity in the group comparison BPD > HC within a) the left MCC (x = -10, y = 4, z = 42) during the anticipation of negative versus neutral stimuli (ang > ant) and within b) left MCC adjacent to the MPFC (x = -13, y = 13, z = 36) during the anticipation of unknown cued versus neutral pictures (auk > ant). The t-values of the contrasts are given in the color bar. Below each contrast, given are the respective time courses (also consider the delay of the hemodynamic response function) and the mean beta-weights including standard deviations within the corresponding regions. (a: (t (34) = 3.62, p < .001), b: (t (34) = 1.93, p < .06).

Functional alterations of the cingulate cortex could represent neural correlates of clinical features in BPD, mainly including affective dysregulation and poor impulse control. Prior reports on BPD have shown an impaired modulation of emotion processing brain circuits by ACC activity (review: Mauchnik and Schmahl, 2010). Further, the role of prefrontal brain regions in BPD has received great attention. A number of studies have consistently demonstrated a failure of "top-down" frontal modulation of limbic brain areas. Especially during emotional provocation there seems to be a decreased inhibitory effect of control processes mediated by the PFC on hyper-reactive bottom-up emotion generating brain areas (Ruocco et al., 2010; Salavert et al., 2011; review: New et al., 2012; meta-analysis: Ruocco et al., 2013). In the current study, BPD patients showed reduced activity in the DLPFC, MPFC and in the cingulate cortex already during emotional anticipation. This pattern was in particular eminent when patients anticipated negative or potentially negative pictures. Foremost, this demonstrates a specific bias and vulnerability with respect to negative valence, which is in line with the BPD psychopathology (Baer et al., 2012). Further, the extended

reductions of brain activity in areas as the MCC, MPFC, and DLPFC in patients during the anticipation of ambiguously cued stimuli could indicate that this condition may be even more prone to dysregulation. Reduced brain activity in cognition-related brain areas in BPD could account for a diminished automatic emotion regulation during anticipation. Compared to healthy subjects, BPD patients may have difficulties to intuitively engage in emotion regulation when being cued to anticipate emotional pictures. Our results suggest that reduced activations in brain regions related to cognition and emotion regulation during emotional anticipation may contribute to the general deficient regulatory processing in BPD patients. Consequently, this dysregulation may add to the symptomatic heightened emotional reactivity during stimulus perception.

In contrast to reductions in cognitive-regulating brain regions, BPD patients exhibited more pronounced brain activity differences in the pregenual ACC during the anticipation of negative stimuli. The pregenual ACC is the most ventral part of the cingulate cortex and is particularly involved in affective processing (Bush et al., 2000). Further, it has strong connections to the amygdala (Palomero-Gallagher et al., 2009; Vogt et al., 2003) and has been associated with dysfunctions in depression (meta-analysis: Sacher et al., 2012) typically showing elevated physiological activity during depressed phases (Drevets, 2001). In our study, a relevant number of patients showed depressive symptoms. However, this is not surprising given that co-occurrence of depression is very common in this illness (Gunderson et al., 2008). Stronger activations in the pregenual ACC during emotional anticipation could therefore be a correlate of heightened emotional involvement in BPD patients. Our findings fit in well with previous work documenting a deficit in connectivity within fronto-limbic networks in BPD. For instance, Kamphausen and colleagues (Kamphausen et al., 2013), who investigated fear inducing anticipation, showed that BPD patients compared to healthy participants exhibited increased connectivity of limbic brain structures with ventromedial prefrontal regions but decreased connectivity of ventral ACC subregions with the dorsally located parts of the ACC. The authors suggested that the functional disconnection between ventral and dorsal prefrontal areas may be part of the neural mechanisms underlying emotional dysregulation in BPD patients. Cullen et al. (Cullen et al., 2011) examined overtly and covertly processing of fearful faces and also found interesting connectivity alterations in the cingulate cortex in BPD. Their findings revealed a lower connectivity between limbic structures and mid-cingulate cortical regions and higher connectivity between limbic areas and the ventral ACC in BPD patients. Moreover, Koenigsberg and colleagues (Koenigsberg et al., 2009a) have examined distancing to negative social cues as a form of emotion regulation and observed less signal change in dorsal subareas of the ACC, further indirectly underpinning a failure of fronto-limbic emotion regulation in BPD. In the current study, increased activations in the pregenual ACC and reduced brain activity in dorsally

located areas of the ACC and MCC during negative anticipation point to a disrupted interplay between emotional and cognitive processes before actual stimulus exposure in BPD.

During negative emotional anticipation, BPD patients additionally showed enhanced activations in the visual cortex, mainly in the lingual gyrus, and also in the PCC. Heightened brain activity in the visual cortex points to enhanced basic sensory processing of cues (Bogousslavsky et al., 1987; Hopfinger et al., 2000), which could be due to modulatory effects of attentional circuits (Kelly et al., 2008; Rauss et al., 2009). Increased activity of visual cortical brain regions in BPD patients was also observed at baseline in a positron emission tomography (PET) study (Salavert et al., 2011). Similarly, Koenigsberg and colleagues (Koenigsberg et al., 2009b) found heightened visual activity in BPD when processing negative emotional stimuli. The authors interpreted their finding as an imbalance between reflexive automatically responding networks and higher level conscious cortical processes, which could correspond to a general "hyper-awareness" in BPD in the context of emotional situations. Our data revealed comparable enhanced activations in visual areas as early as during the anticipation period. This raises the possibility that during anticipation the emotional response for the upcoming perception is primed (Bermpohl et al., 2006). Brain activity in the PCC was also more pronounced in BPD patients compared to controls when anticipating negative pictures. The PCC is associated with autobiographical memory (Bremner et al., 1999) and it is also implicated in evaluating self-relevant sensations (Vogt, 2005) and self-reference in general (meta-analysis: Northoff et al., 2006). In the case of BPD, heightened PCC activation already during the anticipation of unspecific, not self-related emotional stimuli could fit in well with the prominent self-reference in everyday life situations. This aspect may explain a stronger emotional engagement in BPD patients compared to healthy participants. In addition, increased self-reference via the PCC could further involve a visual orienting network that is connected with the parietal lobe (Vogt et al., 1992). This may play a role in the visual preparation for upcoming negative stimuli (Lang et al., 1983), as shown here. In a general sense, current findings are in line with the cognitive approach by Beck & Freeman (Beck and Freeman, 1990) suggesting that individuals with BPD are hyper-attentive to negative emotional signals. More generally, BPD patients may have difficulty in controlling their attention and may be focused on the past, the future, or current self-related processing rather than the task itself, as has been proposed by Linehan (Linehan, 1993a; review: Baer et al., 2012).

Many studies have found an increased activation of the amygdala in BPD in tasks using either the perception of emotional stimuli or self-referential paradigms (e.g. Donegan et al., 2003; Driessen et al., 2004; Herpertz et al., 2001; Limberg et al., 2011). The amygdala plays a central role in the processing of emotional stimuli (meta-analysis: Sergerie et al., 2008), which is consistent with the observed emotional hyper-activity in BPD. However, in the current study, the amygdala was

not differentially active in patients compared to healthy subjects when anticipating negative and potentially negative, ambiguous emotional stimuli. This is in parallel with a PET resting state study (Salavert et al., 2011). One reason for the lack of differential activation in the amygdala in our study could be that the anticipation of emotional stimuli represents a stimulation, which BPD patients are able to cope with. This is also given by the non-social and non-threatening setting of a MR-scanner. Another possible explanation for the lack of differences in the amygdala activation across both groups could be the non-specificity of used stimuli. Subjects were not exposed to emotional challenges or to stressful memories and only a limited number of social and interpersonal stimuli was shown.

One limitation of this study, but from a certain point of view also a strength, is that no behavioral control was used. With this approach, we aimed to avoid interference due to preparatory and executive processes during task performance, as has been done reliably in several prior studies with this task (e.g. Herwig et al., 2007a; Herwig et al., 2007b; Herwig et al., 2010a). As another limitation of the current work, it could be discussed that the patient sample was rather heterogeneous with regard to comorbid diagnoses and medication, although age and gender was perfectly matched with control subjects. Patients taking medication and patients with co-occurring disorders, especially current depression and substance abuse, were included for reasons of representing a typical group of patients with BPD symptoms. Other co-occurring psychiatric symptoms and disorders, such as lifetime MDD (Gunderson et al., 2008) as well as substance use disorders (Zanarini et al., 2011), are very frequent and even typical in BPD. While studying an unmedicated sample could have avoided possible confounds due to medication (Windischberger et al., 2010), it would have meant to investigate a less severely ill and less representative sample of BPD patients. This could have resulted in examining only a subgroup of individuals with BPD leading to less generalizable results.

Our data provides clinical relevance for psychotherapy training. For BPD patients, learning to regulate one's emotions before actual emotional confrontation, could be of advantage in dealing with daily affective situations. For this purpose, different regulation strategies during emotional anticipation could be tested (Braams et al., 2012). In the course of psychotherapy, patients could train to become more aware of affective cues already prior to an emotional situation. In this way, they could learn to better cope with their own tensions and consequently to be able to anticipate following emotional reactions more appropriately. Future studies could investigate whether heightened activity in visual cortical regions in patients with BPD is mainly related to cue sensitivity per se or whether it demonstrates a more perceptive identification of negative cues within a particular context. The question arises whether patients actually are consciously more attentive to negative cues in terms of hyper-awareness (Koenigsberg et al., 2009b) or whether

heightened visual activity is limited to the basic perception level. Investigating interconnections between the visual cortex and emotion processing regions, such as the amygdala (Vuilleumier et al., 2004), in the context of emotional anticipation could provide more insights into the basic emotion processing in BPD. Future studies should also look into the mechanisms of top-down regulation in the prefrontal cortex and cingulate regions but also regarding the heightened activity in the visual cortex by means of connectivity analysis during the anticipation period. Further, it would be interesting to vary the length of the anticipation period or subdivide it to disentangle preparatory processes during emotional anticipation into early versus late anticipation.

In conclusion, neural differences between patients and healthy participants were prominent during the cued anticipation of negative and ambiguous pictures. Our data indicate a negative emotional bias, which fits well with the BPD symptomatology. On the behavioral level, emotional dysfunction in BPD typically is observed in negative emotional states and dysphoric affects (Lieb et al., 2004). Present data suggest that failure to recruit brain areas related to cognitive monitoring is associated with dysfunctional preparatory processes for affective situations. Moreover, we observed a clear bias toward negative cues on the neural level suggesting enhanced visual sensitivity in this regard in patients with BPD. Further, autobiographical self-reference in patients with BPD appears to play a role, although no self-related stimuli are presented. Our results point out that emotional dysregulation already during the anticipation of an emotional stimulus may constitute a contributing factor in BPD pathology.

Acknowledgements

This work was supported by Swiss National Science Funds (SNF) grant No. 3200B0 12120. The SNF had no further role in study design, in collection, analysis or interpretation of the data, in writing the report and in the decision to submit the paper for publication. We are grateful to our subjects, who participated in the study.

Conflict of interest

The authors declare that they have no conflict of interest.

3.3 STUDY 2

Reduced neural differentiation between self-related cognitive and emotional processes in women with borderline personality disorder

Submitted to Psychiatry Research: Neuroimaging

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Abstract

Borderline personality disorder (BPD) is associated with disturbed self-related awareness. Psychotherapeutic interventions using mindfulness techniques have shown effectiveness in reducing clinical symptoms, yet little is known about their underlying neurobiology. In this functional magnetic resonance imaging (fMRI) study, 19 female BPD patients and 19 healthy controls were compared while performing mindful emotion introspection, cognitive self-reflection and a neutral condition. BPD patients displayed a reverse pattern of activation in the right dorsomedial prefrontal cortex (DMPFC) contrary to healthy subjects when directing attention onto their emotional state in contrast to cognitively thinking about themselves. Emotion introspection with respect to neutral recruited motor/premotor regions bilaterally, left inferior frontal gyrus (IFG), and left posterior cingulate cortex (PCC), while cognitive self-reflection activated the right motor- and somatosensory cortex extending into the right supramarginal gyrus (SMG) and superior temporal gyrus (STG) in BPD patients compared to the controls. Results indicate that neural processes underlying self-related emotions and cognitions are not clearly differentiated in BPD patients. This may influence mindfulness ability and could explain some aspects of the typical emotional sensitivity in BPD. Nevertheless, current data support the concept of mindful awareness as a useful treatment intervention in terms of a down-regulation of amygdala activity in BPD.

Keywords: emotion, mindfulness, fMRI, neuroimaging

1. Introduction

Borderline personality disorder (BPD) is estimated to affect about 3% of the general population (Bohus and Kröger, 2011; Trull et al., 2010). It is the most common personality disorder comprising 10% of all psychiatric outpatients and about 20% of inpatients (Leichsenring et al., 2011). Individuals with the diagnosis of BPD suffer from dysfunctional emotion regulation, poor impulse control, and distorted self-image (Lieb et al., 2004). Difficulties specifically concerning awareness, attention, and acceptance towards internal and external experiences play a central role in this illness (Cheavens et al., 2005; Linehan, 1993a; Linehan, 1993b). Several forms of psychotherapeutic interventions are available for patients with BPD (Binks et al., 2006). Amongst those, Dialectical Behavior Therapy (DBT) has proven its efficacy in reducing clinical symptoms in BPD (meta-analysis: Kliem et al., 2010; Linehan, 1993a; Linehan et al., 2006). One critical component of this treatment is the training of mindfulness.

The main goal of mindfulness practice is to reach a mental state in which one is attentive, aware, and accepting (non-judgmental) of the present moment, without becoming over-involved in cognitive or emotional reactions (Kabat-Zinn, 2003). The functional relationship between mindfulness skills and BPD features has been investigated prominently. Evidence suggests that low abilities in mindfulness may account for BPD specific problems in emotion regulation, interpersonal effectiveness, and impulsivity (e.g. Fossati et al., 2011; Wupperman et al., 2008; Wupperman et al., 2009). In a preliminary study examining the mediating effect of mindfulness on BPD characteristics, Wuppermann and colleagues (2013) suggested that typical dysregulated behaviors observed in BPD, as for instance self-injury, substance abuse, suicide attempts, or physical aggression (American Psychiatric Association, 2000), were associated with a low level of mindfulness (Wupperman et al., 2013). The authors assumed a link between mindfulness deficits and BPD symptom severity. However, until now the question of causality remains unanswered.

Mindful self-focused attention has been proposed as an adaptive regulation strategy for BPD patients in dealing with daily stressors. In a laboratory setting, Sauer and Baer (2012) found short-term positive effects of mindful self-focus in patients with BPD, who either were instructed to respond with mindful or ruminative self-focused attention on a distress tolerance task after angry mood induction. The mindfulness group demonstrated more persistence to tolerate distress and reported lower levels of anger (Sauer and Baer, 2012). Despite of the empirical evidence, yet little is known about the underpinnings of the neurobiological mechanisms underlying the effects of mindfulness interventions in BPD.

In healthy participants, a mindful state has been linked to activation patterns in the medial and lateral prefrontal cortex (M/LPFC) (Creswell et al., 2007) as well as in parietal structures underlying attention (Dickenson et al., 2013). The application of mindfulness has been further accompanied by reduced amygdala activations suggesting less emotional arousal (Anderson et al., 2003). Additional support in this context was also provided by a previous own study, where healthy subjects performed a purely internal self-reference task by making themselves aware of their emotions or cognitions (Herwig et al., 2010b). Similarly to the above mentioned findings, focusing on current emotions and bodily feelings in the absence of external stimuli revealed enhanced activations in the M/VLPFC and a reduced amygdala activity. In this way, emotion introspection already appears to have a regulating effect on the amygdala representing a useful mindfulness close technique.

Hence, in this study we intended to examine the neurofunctional network activated by a short mindful intervention, in form of emotional introspection, as opposed to cognitive self-reflection in BPD patients compared to healthy individuals. Mainly, we were interested in whether this mindful state during the emotion introspection condition would result in comparable increased prefrontal and decreased amygdala activations in patients as has been reported in healthy participants (Herwig et al., 2010b). As in patients with BPD unpleasant emotions often arise spontaneously without any explicit external trigger and are experienced as internally generated (Linehan, 1993a), we aimed at focusing on purely internal processes, without external stimulation to avoid differential reactions towards (additional) negative external stimuli in BPD. Considering emotional dysregulation and impulsivity as core features in BPD, we hypothesized to observe limited regulatory control of the amygdala by prefrontal regions during emotional introspection in patients relative to controls. Accordingly, we expected weaker mindfulness effects reflected on the neurobiological level in patients with BPD.

2. Methods

2.1 Participants

A total of 22 female BPD patients were recruited from in- and out-patient clinics at the Zurich University Hospital for Psychiatry, Switzerland, and via mailing lists. Three of these patients had to be excluded from analysis: one patient aborted the experiment and two further patients had to be excluded due to severe movement artifacts in fMRI images (defined as excessive head movements with more than 3 mm in translation and/or rotation). The remaining 19 patients were matched by age with a control group of 19 healthy female volunteers. All healthy controls (HC) were free from psychiatric medication. The two groups did not differ in age (ages 21-43,

BPD M_{age} = 31.11, SD = 6.29; HC M_{age} = 29.37, SD = 4.48; $t(36) = 0.98$, $p = 0.333$). All subjects were right-handed according to a handedness questionnaire (Annett, 1970).

BPD diagnosis was made by the referring physicians of the individual patients using an extensive assessment, which also comprised background and previous psychiatric records. A trained psychiatrist (HS) then confirmed the diagnosis of borderline personality disorder according to ICD-10 and DSM-IV criteria (Sheehan et al., 1998). To determine the current degree of clinical symptoms, BPD patients also completed a short version of the Borderline Symptom List (BSL-23 (Bohus et al., 2009); German version (Wolf et al., 2009a)), which is a self-rating questionnaire assessing state borderline disorder-typical symptomatology. Comorbid Axis-I diagnoses were evaluated using the German version (Ackenheil et al., 1999) of the Mini-International Neuropsychiatric Interview for DSM-IV (Sheehan et al., 1998). Patients were excluded if they met DSM-IV criteria for present or previous bipolar disorder, schizophrenia, or schizoaffective disorder. Due to the known high rate of comorbid psychiatric disorders in BPD (Becker et al., 2000), we did not exclude patients with current depressive episodes (Gunderson et al., 2008). We also included patients reporting occasional use of cannabinoids and alcohol (Zanarini et al., 2011), but excluded patients with an abuse/dependency of opioids and benzodiazepines and other psychotropic drugs. Sporadic low dose use of prescribed tranquilizers/benzodiazepines was allowed (< 3 mg Lorazepam or equivalents per week), though patients were asked to abstain from intake for at least 24 hours prior scanning. Among the BPD group, 14 subjects took psychotropic medication regularly (mainly antidepressants). One patient additionally took pramipexole intermittently (max 0.125 mg/d) for restless legs syndrome. In all patients the dose of medication had been qualitatively and quantitatively stable for more than one month according to documentation at the time of participation. No active substance or alcohol consummation at the time of study was reported. (For demographic details on the patient sample, refer to Table 1.) To assess the level of depression in the patient sample, we obtained ratings on the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and on the Beck`s Depression Inventory (BDI) (Beck et al., 1961). A positive family history of psychiatric disorders was present in 68 % of the patients (mostly depression).

For all participants, general exclusion criteria (previous or current neurological disorders, head trauma, pregnancy, excessive consumption of alcohol, and MRI contraindications) were assessed during a semi-structured clinical interview prior to scanning. The healthy participants were not taking any medication (except for oral contraceptives) and had no previous or current psychiatric disorders. All subjects provided written informed consent after receiving a complete

description of the study and were compensated for their participation. The study was approved by the local ethics committee.

Table 1

Comorbid psychiatric disorders, medication and family history of the included BPD sample

BPD Subjects	Current Comorbid Diagnoses	Psychotropic Medication
1	(history of MDD)	Trazodon, Quetiapine (Lorazepam)[f]
2	MDD, (history of substance abuse)	Duloxetin, Lamotrigin, Doxepin
3	MDD	-
4	ADHD	-
5	MDD (history of eating disorder)	Escitalopram
6	MDD	Citalopram
7	ADHD	-
8	-	Escitalopram, Quetiapine
9	-	Escitalopram
10	-	Venlafaxin, Lamotrigin, Trazodon
11	substance abuse	Lithium, Chlorprothixen
12	MDD	Sertralin
13	MDD	Escitalopram, Lamotrigin, (Lorazepam, Trazodon)[f]
14	ADHD	(Pramipexol)[f]
15	(history of substance abuse)	Escitalopram, (Quetiapine)[f]
16	PTSD, eating disorder	Duloxetin, Quetiapine, Trazodon
17	MDD, ADHD, (history of substance abuse)	-
18	MDD, (history of substance abuse)	-
19	PTSD	Trazodon

[a] BPD: borderline personality disorder
[b] substance abuse: includes alcohol, sedatives, and cannabinoids
[c] MDD: major depression disorder
[d] ADHD: attention deficit hyper-activity disorder
[e] PTSD: posttraumatic stress disorder
[f] given only on a provisional basis, no intake > 48h before scanning

2.2 Self-report measurements

Both groups completed German versions of self-rating questionnaires to examine the degree of depression (Self-Rating Depression Scale, SDS; Zung, 2005), state and trait anxiety (State-Trait Anxiety-Inventory, STAI; Laux et al., 1981), neuroticism and extraversion (Eysenck Personality Inventory, EPI; Eysenck and Eysenck, 1964). All participants were further given two trait mindfulness self-report questionnaires, the Freiburg Mindfulness Inventory (FMI; Walach et al., 2006) as well as the Mindful Attention and Awareness Scale (MAAS; Brown and Ryan, 2003). BPD patients additionally completed a retrospective self-report on traumatic childhood experiences (Childhood Trauma Questionnaire, CTQ; Bernstein and Fink, 1998). Due to the known tendency to experience dissociative symptoms, BPD patients were given the DSS-4 acute questionnaire directly after the fMRI experiment to measure their current dissociative state (short version of Dissociation Tension Scale acute, DSS-4; Stiglmayr et al., 2003).

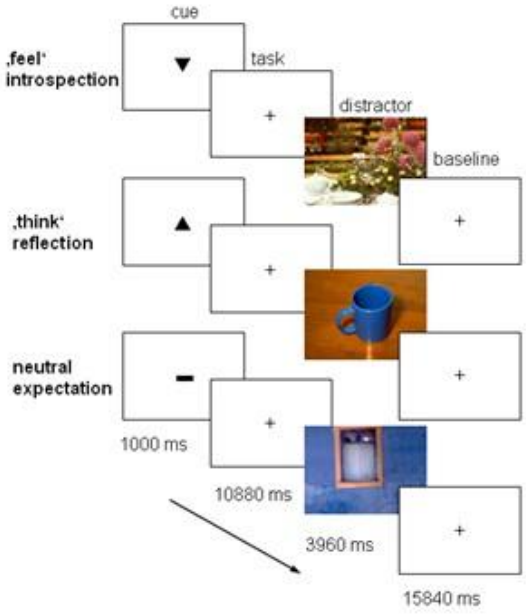

Figure 1. Experimental task. Three conditions were cued: emotion introspection 'feel' (awareness of actual emotions), cognitive self-reflection 'think' ("who am I…"), and a neutral period. Neutral pictures indicated the end of the periods. Durations are indicated in milliseconds.

2.3 Experimental Paradigm

Participants underwent fMRI while performing a task comprised of three conditions in pseudo-randomized order (for reference see Herwig et al., 2010b): cognitive self-reflection ('think'), emotion-introspection ('feel'), and indifference ('neutral'). Before scanning, subjects were instructed and trained as following: for the 'think'-condition: "Think about yourself, reflect who you are, about your goals, etc.", for the 'feel'-condition: "Feel yourself, be aware of your current emotions and bodily feelings", and for the 'neutral'-condition: "Do nothing specific, just await the picture". During the experiment, the periods for each condition were initiated by an indicating cue (think ▲, feel ▼, neutral ▬) and ended with a neutral picture as a distractor (Lang, 1995) (Figure 1). The initial instructing cue was presented for 1000ms and was then followed by the respective condition with a duration of 10880ms, equivalent to 6 TRs (repetition time for the fMRI volumes). The subsequent neutral picture was shown for 3960 ms, equivalent to 2 TRs indicating the end of each trial. Then, a resting period of 8 TRs (baseline, black screen with fixation cross) followed until the next trial started. Each subject performed 12 trials of each

condition. The symbols were intuitively understandable and did not require intensive cognitive resources to understand their meaning. All subjects confirmed that they were able to perform the general task. Intentionally, the task did not comprise any further interfering decisional or motor reaction component. The paradigm was programmed with Presentation™ (Neurobehavioral Systems, USA) and presented via digital video goggles (Resonance Technologies, Northridge, CA).

2.4 fMRI Data Acquisition

Imaging was performed with a 3.0 T GE SignaTM HD Scanner (GE Medical Systems, Milwaukee, USA) using a 8-channel head coil. Echo-planar imaging was performed for fMRI [repetition time (TR)/echo-time (TE)] 1980/32 ms, 22 sequential axial slices, whole brain, slice thickness 3.5 mm, 1 mm gap, resulting voxel size 3.125×3.125×4.5 mm, matrix 64×64, FOV 200 mm, flip angle 70°). First, four dummy scans were acquired to allow for equilibration effects. Then, 584 volumes were obtained per subject. To exclude possible T2-sensitive brain abnormalities, we obtained T2-weighted functional magnetic resonance images. High-resolution 3-D T1 weighted anatomical volumes were acquired (TR/TE 9.9/2.9 ms; matrix size 256×256; 1×1×1 mm resolution, axial orientation) for coregistration with the functional data. After the 10th patient and 10th healthy subject a scanner upgrade occurred, the study afterwards was conducted with identical parameters.

2.5 Psychometric Analysis

To test differences in depression (SDS), anxiety (STAI), neuroticism (EPI-N) and extraversion (EPI-E), and trait mindfulness (FMI, MAAS) between both samples, independent t-tests were performed using the Statistical Package for the Social Sciences (SPSS) version 21. Also, BPD specific questionnaires including borderline symptomatology (BSL-23) and self-reported dissociation (DSS-4) were correlated with each other in the patient sample using Pearson's correlation. A p-value of $p<0.05$, 2-tailed, was considered as significant.

2.6 fMRI Data Analysis

Data were analyzed using BrainVoyager™ QX 2.8 (Brain Innovation, Maastricht, The Netherlands). Preprocessing of the functional scans included motion correction, slice scan time correction, high frequency temporal filtering, and removal of linear trends. To improve data quality, an intensity inhomogeneity correction was carried out on the anatomical data sets. Functional images were superimposed on the 2D anatomical images and incorporated into 3D data sets. The individual 3D data sets were then transformed into Talairach and Tournoux space (Talairach and Tournoux, 1988) resulting in a voxel size of 3 x 3 x 3 mm and then spatially

smoothed with an 8-mm full width at half-maximum (FWHM) Gaussian kernel for the following group analyses. All participants' data were visually inspected, and single trials with fMRI signal artifacts of more than threefold mean signal change amplitude with resulting outliers of beta weights (e.g. due to head movements) were eliminated manually. The design matrix consisted of four predictors representing the three conditions and the distractor (think, feel, neutral, presentation neutral picture). The individual single run design matrix (SDM) was defined for every functional run including motion confounds. The task periods were modelled as epochs.

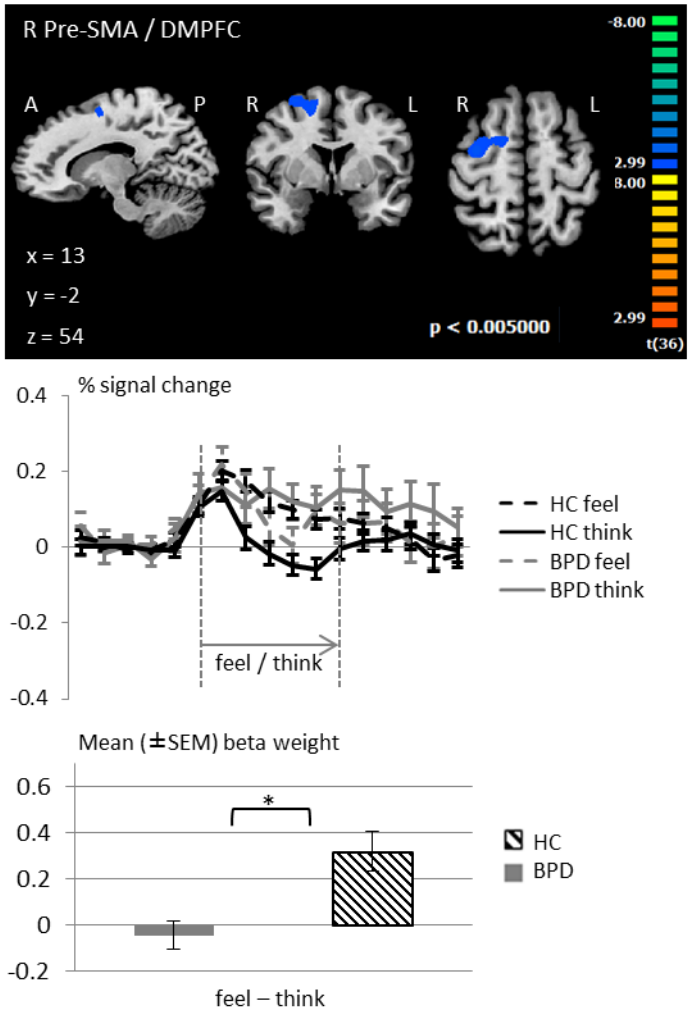

Figure 2. Reduced brain activity in the group comparison BPD > HC within the right pre-SMA/DMPFC (x=29, y=-5, z=57) during the contrast '*feel>think*'. The *T*-values of the contrast are given in the color bar. Below, the respective time courses and the mean beta-weights including standard error of the mean within the corresponding regions are given, (*T*(36)=3.438, *P*<0.0015).

Abbreviations: L=left, R=right, A=anterior, P=posterior, HC=healthy controls, BPD=patients with borderline personality disorder, pre-SMA=anterior portion of the supplementary motor area, DMPFC=dorsomedial prefrontal cortex, SEM=standard error of the mean

The fMRI data analysis, based on the general linear model (GLM), comprised the following steps: First, fixed effects analyses were calculated separately for each subject for the three contrasts comparing the three conditions 'feel versus think', feel versus neutral', and 'think versus neutral' resulting in summary images. The summary images were then subjected to second-level analyses, separately for both, BPD patients (Supplementary table S1) and healthy participants (Supplement 2). In the next step, a random effects whole brain group comparison (rfx) for the specified contrasts ('feel > think', 'feel > neutral', 'think > neutral') was performed. To correct for multiple comparisons, maps with a voxel-wise threshold of *P*<0.005 were submitted to a Monte

Carlo simulation (Goebel et al., 2006) for estimating cluster-level false-positive rates, yielding a corrected cluster-level of $P<0.05$

In addition, we defined a hypothesis driven cubic region of interest (ROI) in the bilateral amygdala. This ROI was centered around x, y, z = (-)22, -6, -12, according to the Talairach Client (Lancaster et al., 2000) and a meta-analysis providing the maximum of emotional activations in this region (Costafreda et al., 2008). From these ROIs, we extracted the individual parameter estimates for the task conditions. For each contrast ('feel>think', 'feel>neutral', 'think>neutral'), we calculated the estimates in each group and between the groups.

3. Results

3.1. Psychometric Results

The BPD and the HC group were well matched for age (detailed demographic and psychometric data see Table 2). The evaluation of psychometric data revealed statistically significant differences between both samples regarding depression, anxiety, and neuroticism as well as in trait mindfulness (FMI, MAAS). Several patients showed clinical symptoms of depression according to the clinical depression scales (HAMD-21 score > 20 in three patients, MADRS score > 20 in four patients, BDI score > 20 in eight patients). Elevated CTQ scores suggested traumatic experiences during childhood, in particular on the emotional level. According to the BSL-23 questionnaire the patient sample showed moderate borderline symptomatology at the time of the experiment. DSS-4 ratings after the fMRI scan propose a moderate degree of dissociative states in the patient group. Scores of the borderline symptom list (BSL-23) significantly correlated with self-reported dissociation (DSS4-acute) ($R=0.733$, $P<0.001$). Our sample of control subjects was in the normal range according to the standard values for questionnaires regarding depression and anxiety (Tanaka-Matsumi and Kameoka, 1986).

Table 2

Demographic and psychometric characteristics of included subjects

	BPD [1] [Min-Max]		**HC** [2] [Min-Max]		***T***	***P***
Sample *n*	20		19			
Mean age, years (*S.D.*)[3]	31.11 (*6.29*) [21 - 43]		29.37 (*4.48*) [21 - 36]		0.98	0.333
Mean scale scores (*S.D.*)						
SDS[4]	60.39 (*11.01*)	*n*= 19	37.89 (*7.73*)	*n*= 19	7.29	<0.001*
STAI[5] - state	45.89 (*11.55*)	*n*= 19	33.21 (*6.07*)	*n*= 19	4.23	<0.001*
STAI- trait	53.32 (*11.88*)	*n*= 19	34.68 (*7.78*)	*n*= 19	5.72	<0.001*
EPI[6]- extraversion	11.00 (*5.68*)	*n*= 18	12.89 (*3.46*)	*n*= 19	-1.22	0.234
EPI- neuroticism	16.78 (*4.61*)	*n*= 18	7.74 (*4.05*)	*n*= 19	6.35	<0.001*
MAAS[7]	50.85 (*17.03*)	*n*= 19	67.95 (*10.44*)	*n*= 19	-3.92	<0.001*
FMI[8]	30.84 (*6.16*)	*n*= 19	39.42 (*5.81*)	*n*= 19	-4.63	<0.001*
BSL-23[9]	1.98 (*.83*) [0.61 - 3.26]	*n*= 19	-			
BDI[10]	20.56 (*8.61*) [6 - 38]	*n*= 18	-			
HAMD-21[11]	14.06 (*6.03*) [2 - 26]	*n*= 18	-			
MADRS[12]	14.00 (*6.10*) [2 - 25]	*n*= 18	-			
DSS-4[13]	2.46 (*2.42*) [0 - 6.75]	*n*= 19				
CTQ[14] - Emotional abuse	15.00 (*5.75*) [0 - 24]	*n*= 19	-			
CTQ - Emotional neglect	22.17 (*5.98*) [12 - 31]	*n*= 18	-			
CTQ - Sexual abuse	4.78 (*2.67*) [3 - 13]	*n*= 18	-			
CTQ - Physical abuse	13.61 (*5.61*) [7 - 30]	*n*= 18	-			

*$P<0.05$

[1] BPD: patients with borderline personality disorder; [2] HC: healthy subjects

[3] S.D: standard deviation

[4] SDS: Self-rating Depression Scale (score <50: not depressed)

[5] STAI: Spielberger State-Trait Anxiety Inventory, X1: state section; X2: trait section

[6] EPI: Eysenck Personality Inventory Neuroticism, EPI-N: neuroticism section; EPI-E: extraversion section

[7] MAAS: Mindfulness Attention and Awareness Scale

[8]FMI: trait mindfulness self-report questionnaire, Freiburg mindfulness inventory
[9]BSL-23: Borderline Symptom List (scores between 0 (=none) and 4 (=very much) represent current borderline symptomatology)
[10]BDI: Beck Depression Scale, self-rating (score <15: not depressed)
[11] HAMD-21: Hamilton Depression Scale (score <15: not depressed)
[12] MADRS: Montgomery - Asberg Depression Rating Scale (score <20: not depressed)
[13]DSS-4: short version of Dissociation Tension Scale acute
[14]CTQ: Childhood Trauma questionnaire (subscale score <5-8: minimal to none traumatic experience, subscale score >=16: severe to extreme traumatic experience)

3.2 fMRI Results

3.2.1 Brain activations in the group comparison (BPD > HC)

During the contrast emotion introspection versus self-reflection (‘*feel>think’*), BPD patients compared to healthy participants showed reduced activity in a large cluster located in the right anterior portion of the supplementary motor area (pre-SMA) and in the superior, medial, and middle frontal gyrus as part of the dorsomedial prefrontal cortex (DMPFC) (Figure 2).

The contrast of the ‘feel’ -condition relative to neutral (‘*feel>neutral’*) was associated with increased brain activity in the right precentral gyrus at the junction of the postcentral gyrus as well as in the left precentral gyrus, both clusters encompassing parts of the bilateral primary motor/premotor cortex, and in the left inferior frontal gyrus (IFG) in BPD patients compared to control subjects. We also found heightened activation in the BPD group in the area of the left posterior cingulate cortex (PCC), mainly in the white matter region, during the same contrast. (Figure 3).

The ‘think’-condition in contrast to neutral (‘*think>neutral’*) revealed increased activations in a big cluster located in the right precentral and postcentral gyrus including the primary motor and somatosensory cortex and in the supramarginal gyrus (SMG) extending into the right superior temporal gyrus (STG) in the BPD group compared to the healthy group (Figure 4). (For details refer to Table 3.)

There were no significant correlations between clinical symptoms in BPD and the beta weights of the above-mentioned significant differential activations in the BPD sample.

3.2.2 Amygdala ROI Analyses

The healthy control group revealed significantly reduced amygdala activation during the contrast ‘*think>neutral*’ and showed a tendency of diminished amygdala activity during the ‘*feel>neutral*’ condition on the right side. On the left side a trend of decreased amygdala activation was observed during both contrasts ‘*feel>think’* and ‘*feel>neutral’*.

The BPD group showed significantly reduced amygdala activation during the contrast '*feel>neutral*' on the right side. Only a trend of diminished amygdala activity was observed during the contrast '*feel>think*' on the left side.

ROI analyses in the predefined amygdala region showed no significant group differences in either contrast (for details refer to Table 4).

Table 3

Whole-brain activations in the group comparison BPD > HC

Anatomic Region	**Lat**	**BA**	**Cluster size mm³**	**Peak Talairach coordinates**			***T*-max**	***P*-max**
				x	**y**	**z**		
a) feel > think (Figure 2)								
Superior frontal gyrus/ Medial frontal gyrus/ Middle frontal gyrus/ Pre-SMA	R	6	1936	29	-5	57	-4.08	0.000240
b) feel > neutral (Figure 3)								
Precentral gyrus/ Postcentral	R	4/40	1462	50	1	48	3.97	0.000325
Precentral gyrus	L	4	1095	-49	-11	51	3.84	0.000482
Inferior frontal gyrus	L	44	1022	-43	16	15	4.04	0.000270
Area of posterior cingulate	L		1749	-13	-38	18	4.03	0.000482
c) think > neutral (Figure 4)								
Big activation cluster subdivided into:			10099	56	-17	39	5.19	0.000008
Precentral gyrus/ Postcentral gyrus	R	4	6692	56	-17	39	5.19	0.000008
Superior temporal gyrus/ Supramarginal gyrus	R	22/42	3221	62	-26	12	4.24	0.000148

FMRI analysis of emotion anticipation in the BPD group versus the control group. Activated areas in a random effects analysis (rfx) with a voxel-wise threshold of $P<0.005$ mean that the contrast differences were greater in the BPD group compared to the control group. Activated minimum cluster size for global error probability (Monte Carlo correction) of $P<0.05$: a) *Feel > think*. Minimum cluster size for global error probability of $P<0.05$: 1385 mm³ (53 functional voxel). b) *Feel > neutral*. Minimum cluster size for global error probability of $P<0.05$: 1055 mm³ (37 functional voxel). c) *Think > neutral*. Minimum cluster size for global error probability of $P<0.05$: 1324 mm³ (51 functional voxel). Abbreviations: BA = Brodmann area, Lat=Lateralization, R=right, L=left, pre-SMA=anterior portion of the supplementary motor area

Table 4

Amygdala ROI analyses

ROI Coordinates x / y / z	Cluster size mm³	feel > think		feel > neutral		think > neutral	
		T	*P*	*T*	*P*	*T*	*P*
a) BPD group versus HC group							
Amygdala R 22/-6/-12	729	-0.30	0.764	-0.12	0.909	0.21	0.838
Amygdala L -22/-6/-12	729	0.90	0.374	0.54	0.592	-0.37	0.715
b) HC group only							
Amygdala R 22/-6/-12	729	0.13	0.898	-1.89	0.075	-2.40	*0.027**
Amygdala L -22/-6/-12	729	-2.07	*0.053*	-1.95	0.068	0.81	0.429
c) BPD group only							
Amygdala R 22/-6/-12	729	-0.37	0.716	-2.17	*0.043**	-1.71	0.104
Amygdala L -22/-6/-12	729	-1.82	0.086	-0.94	0.361	0.29	0.777

Amygdala ROI analyses of conditions *feel>think, feel>neutral*, and *think>neutral* in a) BPD group compared to the control group; b) in the HC group only; and c) in the BPD group only. A *P*-value of $P<0.05$ was considered as significant. Abbreviations: R=right, L=left

4. Discussion

In this study, we investigated the neural correlates of introspecting on one's own present feelings, which is considered to be a basic mindfulness intervention, and cognitive self-reflection in patients with BPD contrary to healthy participants. We observed that emotional introspection compared to cognitive self-reflection was associated with an opposite activation pattern in the right pre-SMA as part of the DMPFC in BPD patients relative to controls. Our study further provides evidence for merging processes between self-related emotions and cognitions in patients with BPD and that these might alter the efficacy of mindfulness. Moreover, current data fosters the principle of mindful awareness as an additional treatment in terms of a diminishing influence on amygdala activity in BPD.

When looking at emotional introspection and cognitive self-reflection, each in contrast to a neutral condition, we observed inconsistencies in the neural processing between self-related emotions and cognitions in BPD. Patients showed increased brain activity in the right motor- and somatosensory region extending into the SMG and STG when thinking about them, and activated the bilateral motor- and premotor regions, left IFG, and the area of the left PCC when directing their attention onto inner feelings and emotions. While activity in the somatosensory cortex has been proposed to reflect the awareness of one's own body states and emotional experience (e.g. Craig, 2002; Critchley, 2005), activations in the motor cortex have been associated with defensive behavior (Barbas et al., 2011). In the framework of BPD, increased brain activity in the somatosensory cortex could be related to the processing of emotional pain (Zanarini et al., 1998) and activations in the motor and premotor cortex could be linked to the 'readiness-to-act' (Koenigsberg et al., 2009b). Co-activations in the SMG and STG further indicate more pronounced self-relevant processing of actions and intentions (Allison et al., 2000, Kircher et al., 2000; Kircher et al., 2001) in BPD patients that might involve parts of a reflexive social processing system in this disorder (Koenigsberg et al., 2009b; Satpute and Lieberman, 2006). Respectively, motor- and somatosensory activity in our study goes in hand with the impulsive tendency to act out following a confrontation with emotional states in BPD. This leads us to assume that even during a purely cognitive self-reflection task BPD patients tend to co-activate an emotional associative state, rather than staying with autobiographical facts only.

During the emotional introspection condition, we observed more pronounced brain activity in the area of PCC in the BPD group compared to the control sample that usually is associated with autobiographical memory (Bremner et al., 1999), evaluation of self-relevant sensations (Vogt, 2005), and self-reference in general (meta-analysis: Northoff et al., 2006). This indicates that even though patients were instructed to focus on current emotions and feelings alone, they as well co-activated cognitive information. In addition to the above, patients with BPD exhibited enhanced brain activity in the left IFG, which on the one hand suggests enhanced self-related processing in emotional context (Liakakis et al., 2011; Morin and Michaud, 2007), but also is attributed to self-referential thinking (Morin and Hamper, 2012). Beyond that, making oneself aware of inner emotions and feelings similarly yielded activations in the premotor and motor regions in patients as was the case during the cognitive self-reflection. Hence, in individuals with BPD, self-relevant processes, irrespective of cognitive or emotional focus, appear to initiate a 'readiness-to-act' network that might give reasons for impulsive responses. Current data suggests that neural processes underlying emotional and cognitive self-relevance are not clearly differentiated between one another in this illness. This would match clinical observations suggesting that patients with BPD tend to relate many things to them personally, which also encounters emotional reactions towards non-emotional stimuli. One additional explanation for

the discrepancies in self-relevant information could be that processes of dissociation interfere. During negative emotional states BPD patients frequently demonstrate more or less intensive dissociative reactions that go along with disruptions of integrated functions as attention and perception of the self and the environment (Korzekwa et al., 2009; Stiglmayr et al., 2008). DSS-acute scores of our patient sample indeed showed elevated dissociative symptoms. This might provide reason for a disturbed discrimination between emotional and cognitive components in self-related context.

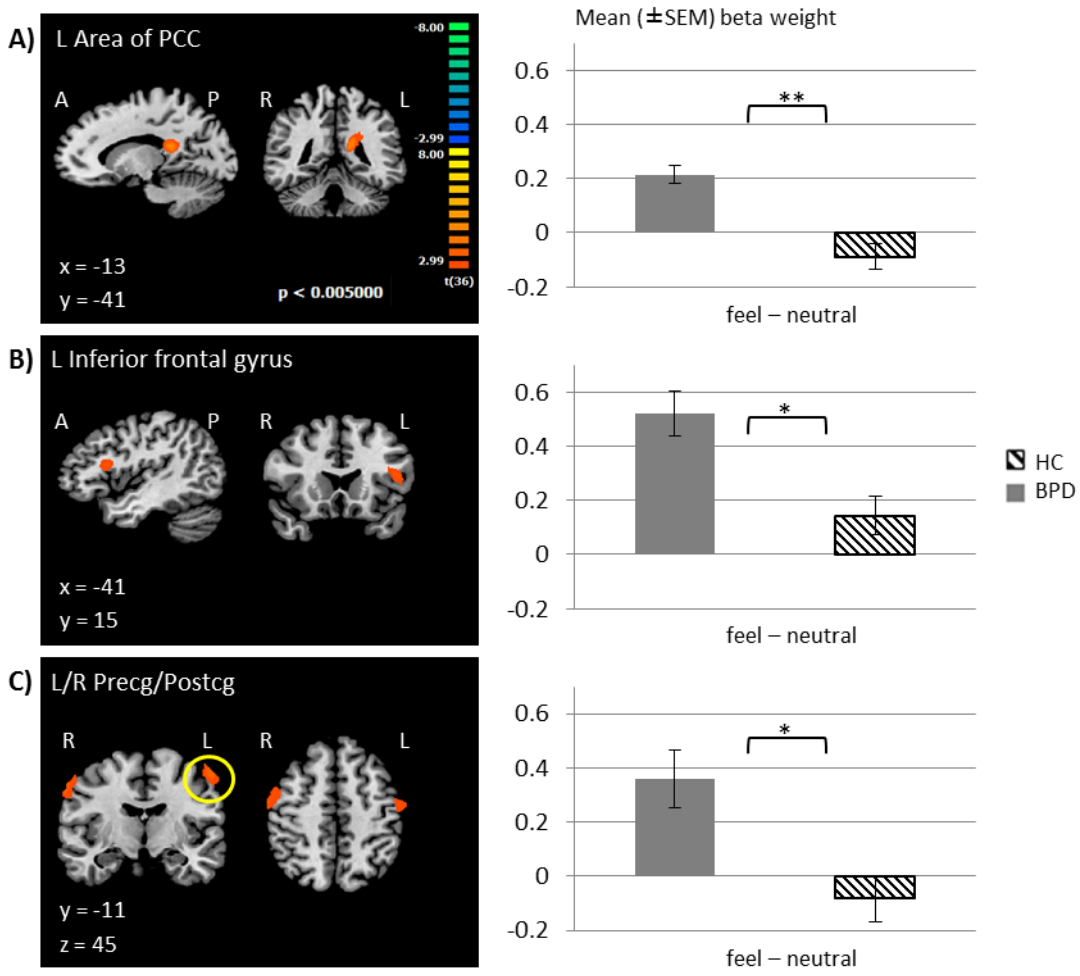

Figure 3. Enhanced brain activity in BPD patients compared to healthy controls during the contrast '*feel>neutral'*. The *T*-values of the contrasts are given in the color bar. Given are the activation clusters and the respective mean beta-weights within a) left area of PCC (x=-13, y=-38, z=18), ($T(36)=5.232$, $P<0.0001$), b) left IFG (x=-43, y=16, z=15), ($T(36)=3.443$, $P<0.0015$), and c) left precentral gyrus (x=-49, y=-11, z=51), ($T(36)=3.255$, $P<0.0025$); (note: the cluster within the precentral/postcentral gyrus: x=50, y=1, z=48 on the right side shows similar beta weights ($T(36)=3.328$, $P<0.0020$)). Error bars indicate standard error of the mean.

Abbreviations: L=left, R=right, A=anterior, P=posterior, HC=healthy controls, BPD=patients with borderline personality disorder, PCC=posterior cingulate cortex, IFG=inferior frontal gyrus, SEM=standard error of the mean

The reverse pattern of brain activity in the pre-SMA including the DMPFC in patients with BPD further points to disturbed differentiation between emotional and cognitive self-related processes. This interpretation finds support in findings on the MPFC imposing that this region is likely to connect between cognitive context and affect (meta-analysis: Kober et al., 2008). While healthy subjects engaged in top-down control mediated by DMPFC activity during the application of a short mindfulness intervention, patients with BPD instead may have had more difficulties to differentiate between emotions and cognitions on the neurobiological level.

Overall, lower activation in the prefrontal cortex (PFC) in BPD patients during the emotional introspection condition is consistent with neuroimaging literature on this disorder (review: Mauchnik and Schmahl, 2010; O'Neill and Frodl, 2012). Various studies have reported that BPD is associated with a diminished capacity for top-down control in modulating currently experienced emotions (meta-analysis: Ruocco et al., 2013). This in particular holds for models using active emotion regulation strategies (e.g. Koenigsberg et al., 2009a; Schulze et al., 2011). Our data suggests that already directing attention onto one's emotional state, which we regard as a very basic form of a mindfulness intervention (Herwig et al., 2010b), is linked to dysregulated top-down processes in BPD. Individuals with BPD typically have lower emotional awareness (Leible and Snell Jr, 2004) and demonstrate problems with controlling and experiencing emotions (Crowell et al., 2009; Linehan, 1993a). Deficits in mindfulness skills in BPD could be related to weaker regulatory mechanisms to begin with (Brown and Ryan, 2003), however can be improved with clinical therapy training (e.g. DBT: Zanarini, 2009). Our patient sample scored significantly lower on mindfulness questionnaires compared to the healthy subjects, which might be associated with the difficulties of top-down regulation by the PFC.

Given the struggle that BPD patients have in modulating their affective responses (Lieb et al., 2004), it is possible that their emotional instability derives, at least in part, from a dysfunction in the neural mechanisms underlying self-related awareness. Incongruities in processing between emotional and cognitive components of self-relevant information evolve, on one side, from an excessive involvement in emotional circuits, but also from increased autobiographical aspects, in general. Although numerous studies have shown shortfalls in emotion regulation on the neural level (e.g. Koenigsberg et al., 2009a; Schulze et al., 2011), we did not find statistically significant group differences in regards of down-regulation of amygdala activity during emotional introspection between patients and healthy participants. Yet, this finding should be interpreted carefully, especially so, given that BPD patients overall demonstrated amydala down-regulation irrespective of condition which might possibly be due to dissociative experience during scanning.

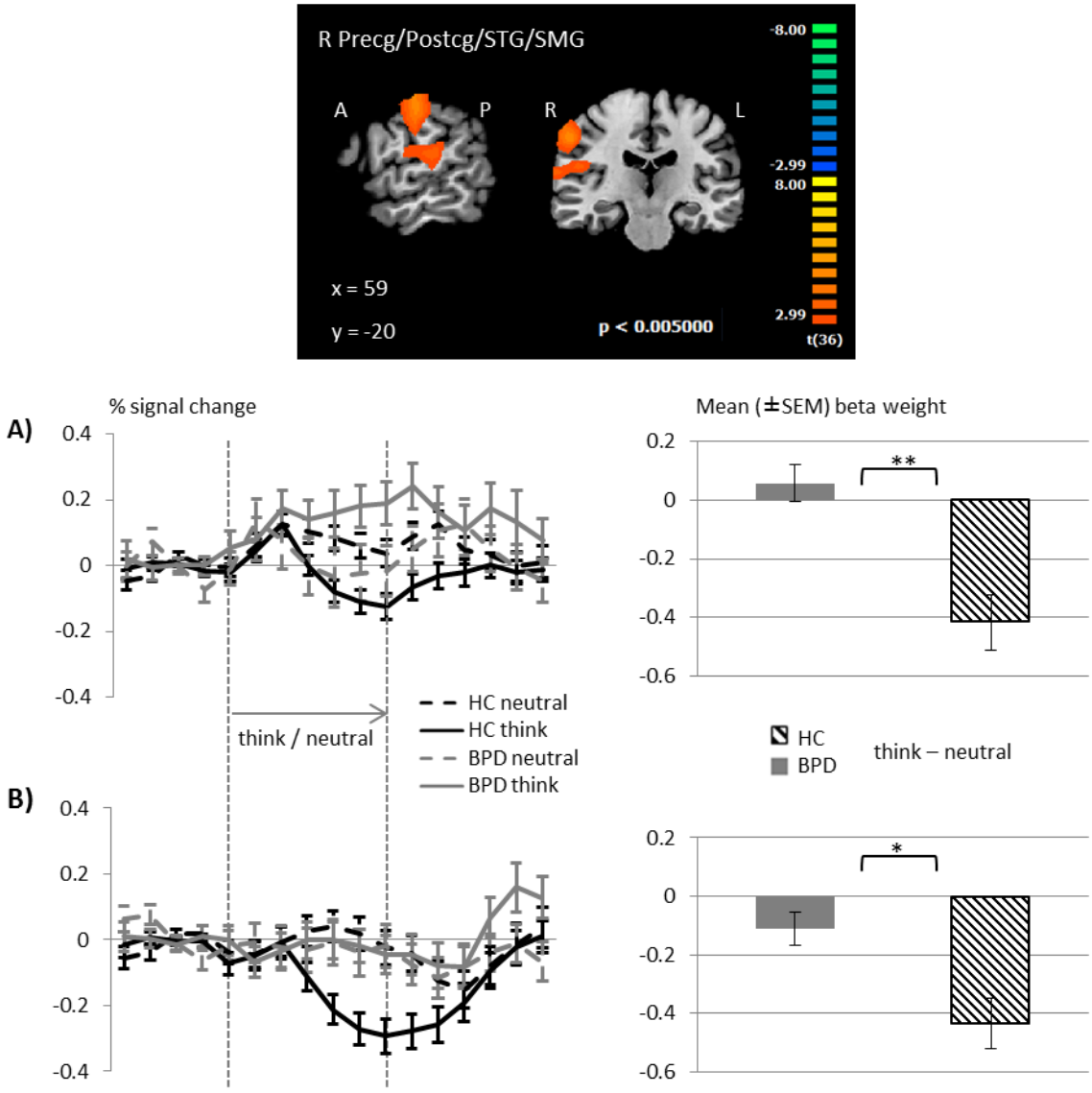

Figure 4. Enhanced brain activity in BPD patients compared to healthy controls during the contrast '*think>neutral*'. The *T*-values of the contrasts are given in the color bar. Given are the activation clusters with the respective time courses and mean beta-weights within a) right precentral gyrus/ postcentral gyrus (x=56, y=-17, z=39), ($T(36)=4.319$, $P<0.0001$), and b) right STG/SMG (x=62, y=-26, z=12), ($T(36)=3.141$, $P<0.0034$). Error bars indicate standard error of the means.

Abbreviations: L=left, R=right, A=anterior, P=posterior, HC=healthy controls, BPD=patients with borderline personality disorder, Precg= precentral gyrus, postcg= postcentral gyrus, STG=superior temporal gyrus, SMG=supramarginal gyrus, SEM=standard error of the mean

One limitation of the current work, but from a certain point of view also strength, is that no behavioral control was used. With this approach, our task postulated purely mental effort applicable in every-day life situations without any interfering experimental behavioral component. As another limitation, it could be discussed that the patient sample was rather heterogeneous with regard to comorbid diagnoses and medication, although age and gender was

well matched with control participants. Patients taking medication and patients with co-occurring disorders, especially current depression, were included for reasons of representing a typical clinical group of patients with BPD. Co-occurring psychiatric symptoms and diagnoses are very frequent and even typical in BPD (Gunderson et al., 2008). While studying an unmedicated sample could have avoided possible confounds due to medication (Windischberger et al., 2010), it would have meant to investigate a less severely ill and less representative sample of BPD patients. This could have resulted in examining only a subgroup of individuals with BPD leading to less generalizable results.

Our data poses clinical relevance for psychotherapy training. Future research should pay increased attention to mindfulness training, while primarily emphasizing on mindfulness deficits in BPD. This may provide better treatment effectiveness in this disorder, for instance in the frame of DBT. Especially, main focus should be put on the differentiation between thoughts, feelings and emotions and how these are experienced. In this context, it would be of interest to investigate whether neurobiological differentiation between emotions and thoughts would improve with successful treatment outcome. Upcoming studies are called upon to shed more light on the neural mechanisms underlying self-awareness in BPD, also with regard to additional emotional stimuli.

In conclusion, current findings provide indications that disturbed representation of self-related emotions and cognitions in BPD patients might affect mindfulness skills and consequently their effectiveness. We found that neurobiological processes between emotional and cognitive components are not clearly differentiated in BPD, which fits in well with the clinical features of the disorder. Moreover, our data suggests that mindfulness training represents a promising tool to reduce emotional arousal in terms of amygdala down-regulation.

Acknowledgements

This work was supported by Swiss National Science Funds (SNF) No. 320030_133009. The SNF had no further role in study design, in collection, analysis or interpretation of the data, in writing the report and in the decision to submit the paper for publication. We are grateful to our patients and healthy volunteers, who participated in the study.

Conflict of Interest

No author has any financial conflicts of interests within this study or article.

3.3 STUDY 3

Real-time neurofeedback using functional MRI could improve down-regulation of amygdala activity during emotional stimulation: a proof-of-concept study

Published in Brain Topography 2014 Jan; 27(1):138-48

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Keywords: real-time fMRI, neurofeedback, amygdala, MPFC, emotion regulation, affective disorders, anxiety, faces

Abstract

The amygdala is a central target of emotion regulation. It is overactive and dysregulated in affective and anxiety disorders and amygdala activity normalizes with successful therapy of the symptoms. However, a considerable percentage of patients do not reach remission within acceptable duration of treatment. The amygdala could therefore represent a promising target for real-time functional magnetic resonance imaging (rtfMRI) neurofeedback. RtfMRI neurofeedback directly improves the voluntary regulation of localized brain activity. At present, most rtfMRI neurofeedback studies have trained participants to increase activity of a target, i.e. up-regulation. However, in the case of the amygdala, down-regulation is supposedly more clinically relevant. Therefore, we developed a task that trained participants to down-regulate activity of the right amygdala while being confronted with amygdala stimulation, i.e. negative emotional faces. The activity in the functionally-defined region was used as online visual feedback in six healthy subjects instructed to minimize this signal using reality checking as emotion regulation strategy. Over a period of four training sessions, participants significantly increased down-regulation of the right amygdala compared to a passive viewing condition to control for habilitation effects. This result supports the concept of using rtfMRI neurofeedback training to control brain activity during relevant stimulation, specifically in the case of emotion, and has implications towards clinical treatment of emotional disorders.

Introduction

The amygdala is activated by negative and positive emotional stimuli (Sergerie et al., 2008), and it is a central target of emotion regulation (Ochsner et al., 2012). Cognitive strategies such as reappraisal and reality checking can reduce activity of the amygdala and related emotion propagating brain regions in emotionally arousing situations (Buhle et al., in press; Diekhof et al., 2011; Ochsner et al., 2012) particularly through top-down control of (dorso)medial prefrontal cortex ((D)MPFC, Delgado et al., 2008; Hartley and Phelps, 2010; Herwig et al., 2007b; Kalisch, 2009; Maren and Quirk, 2004). In affective and emotion regulation disorders, the amygdala is often hyper-active (Etkin and Wager, 2007; Hamilton et al., 2012; Schmahl and Bremner, 2006) and normalizes with successful treatment (Quide et al., 2012). It has been suggested that voluntary control of amygdala activity could represent a method to strengthen emotion regulation and to treat affective and emotion regulation disorders (Schmahl and Bremner, 2006).

Real-time functional magnetic resonance imaging (rtfMRI) can provide direct feedback information from the activity of circumscribed brain regions, networks (Sitaram et al., 2011) or from other physiological measures such as connectivity (Koush et al., 2013; Lee et al., 2012). Subjects can then use this information to learn to control the given signal and in this way to regulate the underlying neural activity (Cox et al., 1995; Goebel, 2001; Sulzer et al., 2013a). Studies using rtfMRI neurofeedback have shown that it is possible to voluntarily self-regulate the activity of various cortical and subcortical brain regions and subregions (for review: Ruiz et al., 2013a).

Voluntary up-regulation of amygdala activity has been the target of multiple neurofeedback studies, despite evidence that reducing activation may be more clinically relevant. For instance, two studies focused solely on amygdala for the purpose of up-regulation, using cognitive strategies such as inducing a sad mood (Posse et al., 2003), or contemplating positive autobiographical memories (Zotev et al., 2011). More clinically-oriented research has included amygdala up-regulation in the broader context of the emotional network, for instance in healthy participants (Johnston et al., 2011; Johnston et al., 2010) and depressed patients (Linden et al., 2012). Both studies in healthy subjects revealed increased activity in the amygdaloid area due to neurofeedback, with a pronounced effect in the ventral striatum in the studies using targets defined by the reaction to positive stimuli (Johnston et al., 2011; Linden et al., 2012). Participants in the above named studies trained amygdala regulation in the absence of any stimuli. However, in everyday life, many problems in mood and anxiety disorders occur when patients anticipate or perceive emotional stimuli, and this emotional experience is associated with an increased activity and dysregulation of the amygdala. Therefore, the voluntary down-

regulation of the amygdala during emotional stimulation might be a realistic model for training emotion regulation and a potential novel path to treat affective and related conditions. Similar approaches have just recently been applied in smokers (Hanlon et al., 2013; Li et al., 2012), when inducing craving by presenting smoking-associated cues to the participants and then training to reduce craving assisted by neurofeedback of the anterior cingulate cortex. Informed by research on affective disorders, we focused on the regulation of the amygdala during emotional stimulation.

Since the amygdala is a bilateral structure, lateralization of specific functions of the region, and thus self-regulation of the putative unilateral area may be appropriate, but such organized laterality is controversial. Meta-analyses on emotion processing resulted in mixed findings, with some showing stronger activations of the amygdala in one hemisphere (Fusar-Poli et al., 2009), whereas others found no clear general laterality effects (e.g. Kober et al., 2008; Sabatinelli et al., 2011; Sergerie et al., 2008). Some studies point to a preference of right amygdala to an early, rapid and possibly more automatic detection of emotional stimuli with less habituation and eventually a preferential reaction to negative stimuli (Baeken et al., 2010; Dyck et al., 2011; Sergerie et al., 2008), whereas the left amygdala is supposed to be involved in more elaborate stimulus evaluation and, for instance, more complex cognitive stimuli such as semantic stimuli (Dyck et al., 2011; Sergerie et al., 2008). In patients suffering from affective and anxiety disorders, several meta-analyses have shown similarly mixed results (stronger activity on the right side: Etkin and Wager, 2007; Fitzgerald et al., 2008; Groenewold et al., 2013; Hattingh et al., 2013, left side: Sacher et al., 2012, bilateral: Hamilton et al., 2012). Due to our focus on regulation of early, less elaborate reactions to 'hard-wired' stimuli as well as the potential future transfer to patients with affective disorders, we selected the right amygdala as our target region.

As such, our goal was to develop and examine the feasibility of using online neurofeedback to assist participants in self-reduction of amygdala activity. In addition to neurofeedback, six healthy participants were exposed to negative faces as emotional stimulation, a robust technique for eliciting amygdala activation (Breiter et al., 1996; Whalen, 1998, meta-analysis: Sabatinelli et al., 2011), with a supposed "hard-wired" evolutionary basis (Adolphs, 2008; Emery, 2000; Liddell et al., 2005). We used color-based instead of motion-based feedback typical in rtfMRI studies (Sulzer et al., 2013a), since it may interfere with attention to the most salient aspects of emotional facial stimuli (i.e. eyes and mouth) for amygdala activation (e.g. Adolphs et al., 2005; Ellis, 1975; Morris et al., 2002). As this study aimed at proving the principle of rtfMRI neurofeedback-assisted training during emotional stimulation, we examined the effects of repeated training sessions on the individual ability to down-regulate the amygdala in contrast to a "view" condition without regulation. We hypothesized enhanced downregulation of right

amygdala activity in the "regulate" compared to the "view" condition over four rtfMRI neurofeedback training sessions.

Material and Methods

Participants

We examined six healthy participants (4 female, 2 male, mean age 26 years, standard deviation 3.8 years). The participants were recruited via personal contact and email-lists. All participants were healthy, as was assessed with semi-structured interviews and checklists (abbreviated version of the Mini Neuropsychiatric Interview (MINI, Sheehan et al., 1998)) performed by an experienced psychiatrist (ABB). Exclusion criteria were prior and current neurological and psychiatric illnesses; pregnancy; intake of any medication (except for oral contraceptives) or psychotropic drugs including excessive consumption of alcohol (regular intake of > 7 units/week), cigarettes (> 1 pack/day) and caffeine (> 5 cups/day) and general contraindications against MRI examinations. After each feedback run, subjects were asked via microphone regarding drowsiness and tiredness. We further interviewed the participants after each completed session in a structured interview on drowsiness and tiredness, general feelings, specific experiences and the strategies used for regulation. Each subject completed four sessions. The mean period between sessions was 6.8 days. The study was approved by the ethics committee of the canton of Zürich and conducted in compliance with the Declaration of Helsinki (World Medical Association 2008). All participants gave written informed consent and received financial compensation.

Experimental task

Functional localizer (Fig. 1a)

The amygdala was first localized functionally in each participant in each session. Participants were presented negative emotional faces from the Karolinska Directed Emotional Face Set (Lundqvist et al., 1998) and, for contrast, neutral and low arousing pictures from the International Affective Pictures System (IAPS, Lang, 2005) for individually localizing the amygdala. Non-facial neutral pictures from the IAPS were chosen to increase the contrast to the negative emotional pictures with respect to amygdala activation (Sabatinelli et al., 2011). Pictures were presented in a blocked design with 10 pictures in each block, each shown for 2 sec. After each block a baseline period (fixation cross) of 30 sec allowed the blood oxygen level dependent (BOLD) signal to level off before the next condition (total duration of the localizer: about 6 min). In each block, pictures of the same gender and the same emotional valence were

presented. To achieve intensive activation of the amygdala in the localizer, only fearful, sad and angry expressions were shown. Subjects were instructed to passively observe the pictures. In total, nine trials of pictures and baseline were shown in a pseudo-randomized counterbalanced order, three depicting neutral pictures, and six with emotional faces.

Feedback task (Fig. 1b)

The feedback task (Fig. 1b) was constructed similar to the localizer task in a blocked design, but without neutral IAPS stimuli. Each single feedback period consisted of emotional faces of the same gender and the same emotional valence (angry, fearful). Within one run, 16 periods of 20 sec duration, each containing 10 pictures of 2 sec duration, total duration of a run about 12 min, were shown. Prior each period, a short written instruction ("view", "regulate", duration 1 sec) was given on the screen. After each single feedback period a baseline period (fixation cross) was implemented for 29 sec (baseline + instruction = 30 sec). Each run consisted of six periods of the "view" conditions and ten periods of the "regulate" conditions. This increased weighting of the "regulate" condition was chosen to reduce habituation and to improve training effects. Due to the length of the total measurements and the task, we asked the participants after each run about their subjective tiredness and drowsiness. Depending on their response, they performed two or (optimally) three feedback runs in each session (mean number of feedback runs per session: 2.42). Pictures were randomized and in each session 50% of the pictures were "new", prior unseen pictures to prevent habituation and effects of familiarity. Feedback of amygdala activity was recorded from the region identified in the localizer task and was given to the participant during both "regulate" and "view" conditions in form of changing colour of blocks on both sides of the pictures. They were positioned bilaterally at the height of the eyes of the depicted faces to avoid distraction to either side or otherwise away from the eyes (the most significant aspects of faces). Although previous rtfMRI studies use motion-based feedback (Sulzer et al., 2013a), the distraction from the stimulation provided by the motion was not appropriate for this study.

Task instruction

Prior the first session, all participants were given written instructions and were informed on the 4-6 sec delay of the feedback reaction due to the delay of the hemodynamic response function. Participants were instructed to apply cognitive control by reality checking such as "these are pictures, these are actors, this is an experiment" (Herwig et al., 2007b). After each session, subjects were interviewed on the used strategies, their experiences and subjective performance during feedback and regulation.

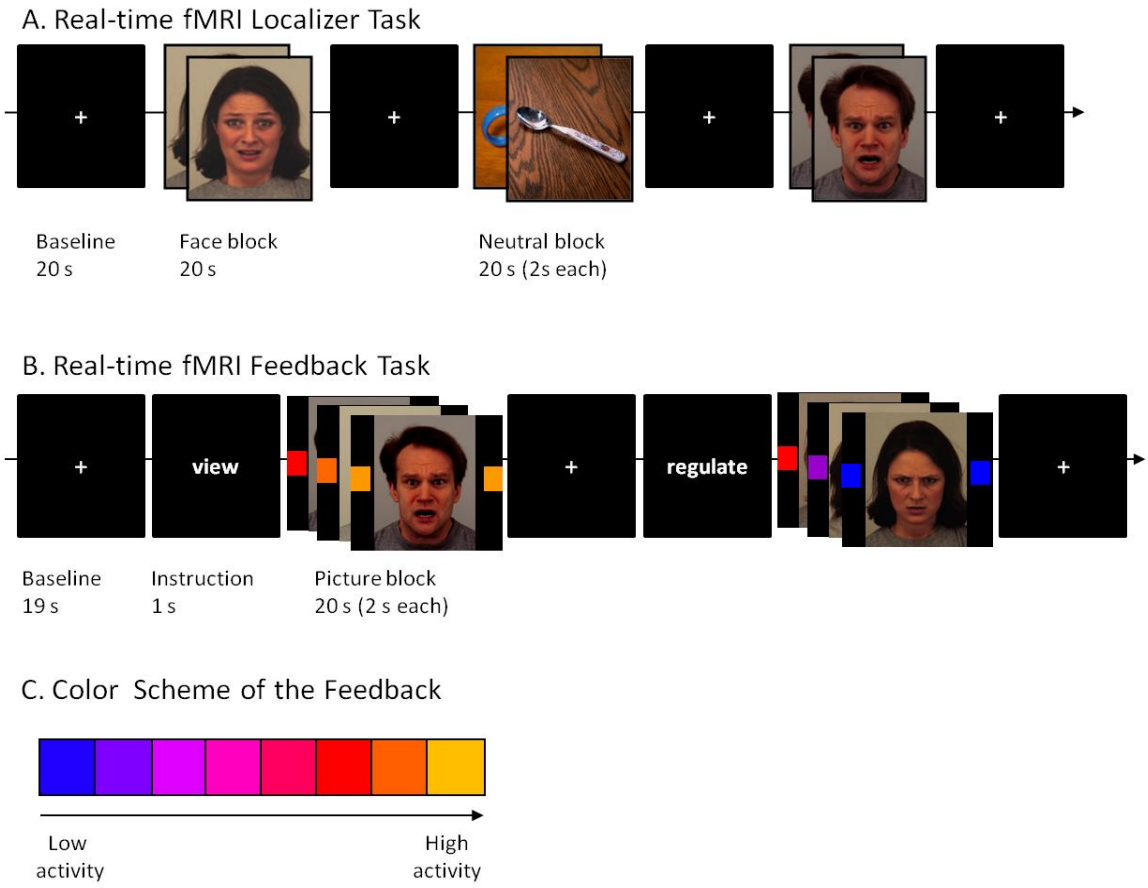

Fig1. Tasks and coding of amygdala activity

Image acquisition

Imaging was performed with a 3.0 T Philips Achieva Scanner (Philips Medical Systems, Best, The Netherlands, equipped with an 8-channel receive head-coil array). Echo-planar imaging was performed for functional MR imaging (repetition-time (TR)/echo-time (TE) 2000/25 ms, 30 sequential axial slices, whole brain, slice thickness: 3.0 mm, gap 1.1 mm, field of view (FOV): 240x240 mm, matrix 80x80 voxel, resulting voxel size: 3x3x3 mm, axial orientation, SENSE-factor: 2.0). The localizer run consisted of 170 volumes, the feedback runs of 330 volumes each. High-resolution 3-D T1 weighted anatomical volumes were acquired (TR/TE 6.73/3.1 ms; voxel size 1x1x1 mm, 145 slices, axial orientation) for coregistration with the functional data. Stimuli were presented via digital goggles (Resonance Technologies, Northridge, CA).

FMRI analysis and statistics

Online real-time analysis and statistics

Functional data were analyzed online during fMRI with TurboBrainvoyager (TBV) Version 3.0.0 (Brain Innovation, Maastricht, NL). The processing has been described previously (Goebel 2001; Caria et al. 2010). Real-time data analysis comprised incremental 3D motion detection and correction and drift removal and resulted in incrementally computed statistical maps based on the General Linear Model (GLM) and event-related averages. These analyses were performed in native space.

After the localizer scan, a region of interest (ROI) was placed in the anatomical region of the right amygdala extending over 3 slices (= 9 mm) using a t-value threshold of 2.0. The size and centers of these localizer ROIs are given in Table 1. The individual maximal activation for the calculation of the colour range for the feedback was determined from the event related averaging of the individual amygdala ROI. This event-related average is calculated by TBV in parallel to the typical averaging performed in the analysis of event-related potentials according to the formula (value –baseline) / baseline. As the sessions were each separated by about a week, we determined the specific ROIs individually for each session. The BOLD signal of these ROIs was extracted during the feedback sessions by TBV and then transferred to Visual Studio, where the information was converted into the change of the color blocks as described above.

To provide a sensitive and also reliable and informative feedback of the brain activity and the effects of regulation, we fitted the range of the feedback colours to the individual maximal activation. The inter-individual variability of stimulus-related BOLD responses can vary by a factor of more than two (e.g. Handwerker et al., 2004; Liu et al., 2011; Raemaekers et al., 2012). Using a fixed assignment of % signal change to a colour would in participants with a high amplitude of BOLD signal change have resulted in quickly reaching the ceiling of the colour spectrum but not getting a fine-grained feedback on their performance, whereas in participants with a low amplitude their activation and regulation would have been represented by only slight colour changes in the blue-violet colour range. Therefore, we computed the individual reactivity of the amygdala from the localizer using the average percent signal change from baseline in the chosen amygdala ROI. This was entered in the computation of the range of colours of the feedback blocks as maximum value (= bright orange), determined on a subject-wise basis during the localizer. The feedback was first normalized based on the percent signal increase from the previous baseline condition (last five volumes), then three-point averaged (averaging the current value with the previous two) to reduce noise and strong fluctuations of the feedback (in

parallel to Sulzer et al., 2013b). This feedback signal was computed and presented by custom-made software running on VisualStudio® (Microsoft, Redmond, WA, USA).

Offline analysis and statistics

After scanning, the acquired images were processed offline using BrainVoyagerQX 2.4 (Brain Innovation, Maastricht, NL, Goebel et al., 2006). Standard preprocessing with BrainVoyagerQX included motion correction, slice scan-time correction, high-frequency temporal filtering and removal of linear trends (as described in Herwig et al., 2007b). All individual functional datasets were checked for excessive head movements (datasets would have been excluded if sudden movements exceeded 3 mm in any direction, however no datasets exceeded this limit). Functional data were co-registered with the individual T1-weighted 3D structural data, resulting in a functional dataset. Structural and functional data were transformed into Talairach space and spatially smoothed with a 4 mm full-width half-maximum Gaussian kernel for subsequent within- and between-subject analysis. The relatively small kernel was chosen with respect to the small size of the region of interest. Standard general linear model (GLM) analysis was performed using three regressors of interest (rest, regulate and view) convolved with the hemodynamic response function, and six head movement regressors representing translation and orientation as regressors of no interest.

Learned regulation was determined as a significant linear decrease in ROI activity over sessions. The primary outcomes, amygdala parameter estimates (beta values), were extracted from the defined functional area within the right amygdala, adapted to each session. The anatomical area of the amygdala was defined based on structural images, confirmed using the Talairach client (Lancaster et al., 2000) and the Talairach atlas (Talairach and Tournoux, 1988), and confined to a 20x20x20 mm volume. Beta values were then extracted from functional ROIs, obtained from the contrast "view>regulate" in each session for each participant, with a statistical threshold of $p<.005$ (uncorrected, Talairach-coordinates and size: see Table 2). Comparing the "regulate" to the "view" condition instead of a comparison to "rest" ensured control for the stimulation and its associated effects, as well as habituation to the environment, habituation to the stimuli and effects of exhaustion and drowsiness. The beta values were then used in a single factor (session, four levels) repeated measures ANOVA, controlling for the varying size of the amygdala ROI, including confirmation of normality (Kolmogorov-Smirnov) and sphericity (Mauchly) using SPSS 21 (IBM, Armonk, NY). Post-hoc two-tailed paired t-tests and effect sizes (Cohen's d) were calculated in those comparisons where the main effect of session was significant.

Secondary post-hoc repeated measures analysis was conducted on a DMPFC ROI to examine whether learned down-regulation also involved central emotion regulation network represented

by the DMPFC (Buhle et al., 2013; Diekhof et al., 2011; Kalisch, 2009). To test for related effects in the left amygdala, we also analyzed activation in an anatomically defined cubic ROI (edge length 9 mm, volume 729 mm3) in the left amygdala centered at x/y/z = -19/-8/-15 using repeated measures analyses and bivariate correlations with the respective beta values of the right amygdala ROIs. Furthermore, to test for non-specific effects of training and repeated exposure to the task in rather unrelated brain regions, we also computed post-hoc repeated measures analyses on ROIs positioned in the primary visual (V1) and somatosensory (S1) cortex. The DMPFC was individually defined due to the contrast "view>regulate" according to literature (Buhle et al., 2013; Diekhof et al., 2011; Kalisch, 2009). The sum of the individual ROIs covered the medial and superior frontal gyrus (Brodmann area 6, placed around the mean (SD) center coordinates x/y/z = -2 (7.1) / -5 (8.8) / 57 (8.6), maximal extension: x = 13 to -18 / y = 12 to -23 / z = 38 to 70); mean size 2795 mm3 (60-7989 mm3 (Supplemental Figure 1)), bordering caudally to the anterior and middle cingulate cortex (BA 31, 32), frontally to the upper part of the superior frontal gyrus (BA 6) and occipitally to the precentral gyrus (BA 4)). Both V1 and S1 were defined using spherical ROIs, the former centered at x/y/z =±11/-90/-3, (16 mm diameter) and the latter at x/y/z = ±33/-24/62 (10 mm diameter).

Modulatory effects of neurofeedback on amygdala activity were investigated using a psychophysiological interaction analysis (PPI, Friston et al., 1997), with the expectation that neurofeedback modulates connectivity between the amygdala and DMPFC (Kanske et al., 2011). As typical in a PPI analysis, time courses for each amygdala ROI were extracted, followed by its dot product with the two task regressors (i.e. view and regulate). The interaction regressors of interest were included in a design matrix along with task, seed region time course, and head movement regressors of no interest. PPI analysis of each subject was restricted to the DMPFC ROI obtained earlier. The resulting beta values were extracted from the DMPFC and evaluated for significant changes using a repeated-measures ANOVA.

Results

The subjects used mostly cognitive (i.e. reality check) and attentional strategies (thinking about something else, thought distraction).

There was no significant effect of session on the size of the amygdala ROI resulting from the localizer session ($F(3,15) = .119$, $p = .747$, partial $\eta 2 = .029$) as well as no significant linear effect of session on the activity of the amygdala during the localizing session ($F(3,15) = 1.220$, $p = .320$, partial $\eta 2 = .196$). The respective regions were then used as source of the feedback signal. The analysis of probabilistic overlap between these feedback ROIs revealed a maximal probabilistic

overlap of 50%, and at a threshold of > 35% overlap we found one cluster centered at x/y/z = 20/-2/-12 with a volume of 145 mm3.

The average (SD) Talairach coordinate of all ROIs used in the analysis of the regulation effect of all subjects and sessions was x = 21 (4.5), y = -1 (4.6), z = -16 (5.6), mean size 1213 mm3. The repeated measures ANOVA on the beta weights of the contrast "view>regulate" in the right amygdala ROI revealed a significant main effect of the factor session ($F(3,12) = 4.771$, $p = .021$, partial $\eta 2 = .544$). The repeated measures ANOVA on this contrast in the DMPFC ROI was not significant ($F(3,15) = .638$, $p = .576$, partial $\eta 2 = .120$). The effect of "session" on amygdalar activity during the viewing condition alone (beta-weights calculated against baseline) was not significant ($F(3,15) = .466$, $p = .525$, partial $\eta 2 = .085$). The detailed analysis of the main effect of the "session" in the amygdala ROI showed that:

Table 1 Localizer regions of interest (ROIs). Given are the Talairach coordinates of the center

Subject no.	Session	Talairach X/Y/Z	Vol (mm^3)	% Signal change localizer
01	1	19/−1/−12	478	1.0
	2	18/−6/−9	1,996	0.8
	3	23/−1/−14	2,083	0.8
	4	21/−1/−11	477	1.0
02	1	23/−6/5	1,798	1.2
	2	19/−2/5	2,151	2.0
	3	21/−2/4	918	1.5
	4	23/−8/5	2,269	1.7
03	1	26/1/−11	1,064	1.3
	2	22/−5/−10	2,772	1.2
	3	27/−4/−12	963	1.0
	4	21/1/−8	659	1.4
04	1	19/1/−8	797	1.0
	2	21/2/−7	124	0.7
	3	−19/−10/−8	224	1.0
	4	−22/−5/−9	242	0.5
05	1	20/−5/−10	442	1.8
	2	20/−0/−11	623	1.8
	3	24/−1/−11	275	1.8
	4	21/0/−15	862	1.0
06	1	25/6/−12	363	0.8
	2	27/4/−13	891	0.8
	3	22/2/−11	354	0.7
	4	24/−2/−13	1,223	0.6

a) all subjects managed down-regulation of amygdala activity assisted with rtfMRI neurofeedback during stimulation with negative emotional faces (Fig. 2a, b, Table 2) and
b) this down-regulation increased and therefore improved significantly from session 1 to 4 (two-tailed paired t-test: $t(5) = -4.924$, $p = .004$, mean difference = -.236, standard deviation = .117, effect size $d = 1.34$, mean change 30%, Fig. 2a, Table 1). On the individual level, this effect was significant in five of the six subjects, only in one subject the trend-line over all sessions did not significantly differ from zero slope (Fig. 2b).

In the single individual datasets, the DMPFC was more active during regulating versus passive viewing in 23 of 24 sessions, but without a significant and consistent effect of repeated training.

Table 2 Reduced activity in the contrast "regulate > view" ($p < 0.005$) in the amygdala in each subject and each session (paired t test)

Subject no.	Session	Talairach X/Y/Z	Vol (mm^3)	r > v beta weights mean (SE)	r > v t/p
01	1	27/−4/−6	849	−0.528 (0.089)	−5.93/<0.000
	2	24/−8/−9	2,097	−0.657 (0.091)	−7.21/<0.000
	3	21/−4/−15	3,716	−0.847 (0.096)	−8.83/<0.000
	4	27/1/−18	1,777	−0.905 (0.117)	−7.71/<0.000
02	1	16/−9/−18	181	−0.461 (0.093)	−4.98/<0.000
	2	19/−1/−18	2,637	−0.637 (0.094)	−6.75/<0.000
	3	22/4/−22	1,634	−0.681 (0.093)	−7.32/<0.000
	4	23/9/−5	264	−0.738 (0.115)	−6.39/<0.000
03	1	19/−3/−11	1,396	−0.795 (0.094)	−8.43/<0.000
	2	16/−5/−14	4,138	−0.95 (0.094)	−10.10/<0.000
	3	17/−4/−10	1,540	−0.616 (0.096)	−6.38/<0.000
	4	18/−2/−11	1,319	−0.879 (0.117)	−7.54/<0.000
04	1	30/−7/−25	72	−0.32 (0.103)	−3.11/0.002
	2	17/−4/−22	298	−0.359 (0.089)	−4.04/<0.000
	3	22/2/−17	362	−0.428 (0.111)	−3.86/<0.000
	4	29/4/−19	501	−0.668 (0.157)	−4.26/<0.000
05	1	24/0/−16	73	−0.327 (0.111)	−2.95/0.003
	2	25/3/−12	28	−0.522 (0.113)	−4.61/<0.000
	3	15/−2/−19	313	−0.651 (0.111)	−5.87/<0.000
	4	24/7/−26	120	−0.515 (0.171)	−3.02/0.002
06	1	21/−2/−13	378	−0.805 (0.113)	−7.14/<0.000
	2	19/−5/−22	2,178	−0.905 (0.113)	−8.04/<0.000
	3	18/−1/−20	1,181	−0.848 (0.110)	−7.73/<0.000
	4	13/0/−19	1,899	−0.945 (0.108)	−8.76/<0.000

The post-hoc analysis of correlations between right amygdala and the anatomically placed left amygdala ROI showed rather high correlations in the viewing condition of the corresponding sessions (mean r = .71, ranging from .47 to .92), whereas the correlations in the regulate condition were lower and more variable (mean r = .36, ranging from .14 to .81). There was no significant effect of the factor "session" in the repeated measures ANOVA in the left amygdala ROI (Table 3).

The repeated measures ANOVA in the other ROIs revealed no significant effect in either condition (Table 3). There was no significant linear effect of the factor "session" on size of the amygdala ROI used in the post-hoc analysis of the feedback session ($F(3,15) = 1.176$, $p = .339$, partial $\eta 2 = .227$). Within the participants, the sizes of the localizer ROIs and of the post-hoc ROIs of the feedback sessions were not significantly different ($t(23) = 1.128$, $p = .271$). There was no significant effect of the training on PPI between the amygdala and the DMPFC ROIs during the "regulate" condition ($F(3,15) = .018$, $p = .899$, partial $\eta 2 = .004$) as well as during the "view" condition ($F(3,15) = 2.51$, $p = .638$, partial $\eta 2 = .048$).

Table 3 Results of the repeated measures GLM in the other ROIs (main effect of the factor "session") during the regulation and the viewing condition

ROI	Talairach X/Y/Z	F(3,15)	*p*	Partial η^2
Regulate condition				
Dorsomedial prefrontal cortex[a]	−2/−3/55	1.379	0.287	0.216
Visual cortex R (V1)	11/−90/−3	0.357	0.785	0.067
Visual cortex L (V1)	−11/−90/−3	0.437	0.730	0.080
Sensory cortex R (S1)	33/−24/62	1.064	0.394	0.176
Sensory cortex L (S1)	−33/−24/62	0.118	0.948	0.023
Anterior insula/VLPFC R	34/16/4	2.063	0.148	0.292
Anterior insula/VLPFC L	−34/16/4	2.716	0.082	0.352
Amygdala L	−19/−8/−15	1.926	0.169	0.278
View condition				
Dorsomedial prefrontal cortex[a]	−2/−3/55	1.513	0.252	0.232
Visual cortex R (V1)	11/−90/−3	2.042	0.140	0.276
Visual cortex L (V1)	−11/−90/−3	2.001	0.157	0.247
Sensory cortex R (S1)	33/−24/62	0.315	0.814	0.059
Sensory cortex L (S1)	−33/−24/62	0.388	0.764	0.072
Anterior insula/VLPFC R	34/16/4	1.147	0.362	0.187
Anterior insula/VLPFC L	−34/16/4	2.447	0.104	0.329
Amygdala L	−19/−8/−15	1.161	0.357	0.189

All other ROIs were created based on a priori anatomical coordinates. In all ROIs, normality and sphericity were not violated (Kolmogorov–Smirnov test and Mauchly test)

[a] Individual ROIs

Discussion

To our knowledge, this study is the first one to introduce the concept of rtfMRI neurofeedback training for the down-regulation of the amygdala during stimulation with emotionally negative contents. Repeated training successfully enhanced the subjects' ability to down-regulate their own amygdala activity while being stimulated with negative emotional faces. Down-regulation of the right amygdala in all subjects in the first session is in parallel with previous studies on emotion regulation, showing reduced emotional arousal on the physiological (Ochsner and Gross, 2005) and the neural level, particularly the amygdala (Diekhof et al., 2011; Herwig et al., 2007b; Herwig et al., 2010b; Kanske et al., 2011; Maren and Quirk, 2004). However, effects in the first session cannot be specifically attributed to neurofeedback effects, but have been shown before (e.g. Herwig et al., 2007b; Ochsner and Gross, 2005; Phan et al., 2005) with cognitive emotion regulation strategies such as reality check. Indeed, the improved down-regulation across the sessions, comparing "view" and "regulate" condition, implies a specific training effect of the neurofeedback compared to the purely psychological application of emotion regulation strategies.

Habituation effects, e.g. to stimuli and scanning, would have resulted in a reduced amygdala activation in the "view" condition, which served as an internal control condition (and where we found no effect of the factor session). Habituation could therefore have rather diminished the down-regulation and training effect in the present study design. Additionally, ensuring that 50% of pictures during each session had not been seen previously, primarily counteracted possible habituation.

The results in the amygdala support the feasibility of rtfMRI neurofeedback training for emotion regulation training. Models of emotion regulation might have suggested an increase of prefrontal cortical activations over the sessions (Diekhof et al., 2011; Maren and Quirk, 2004; Ochsner et al., 2012). The DMPFC was active during regulation, but without a consistent modification across the sessions. We also found no changes in connectivity between DMPFC and amygdala over sessions. Therefore, there is insufficient evidence to support the hypothesis that the central emotion network is involved in this training of self-regulation. This could possibly be explained by the subjects' different and adapting strategies, which could have reduced and interfered with localized effects of learning on brain activity. Studies on brain changes during training and learning revealed early increased and more extended activations (Karni et al., 1995), which later, with consolidation, decreased again (De Weerd et al., 2003). It is possible, that weekly sessions did not capture the zenith of this curve. Thus further research on the aspect of training emotion regulation over time is needed. However, besides this temporal issue it is possible that not so much the DMPFC but perhaps other brain regions such as VMPFC or VLPFC play a stronger role in this regulatory context. Due to the limited power of our current study which focused on feasibility aspects particularly with regard to the amygdala further analyses should be carried out in future studies in larger samples.

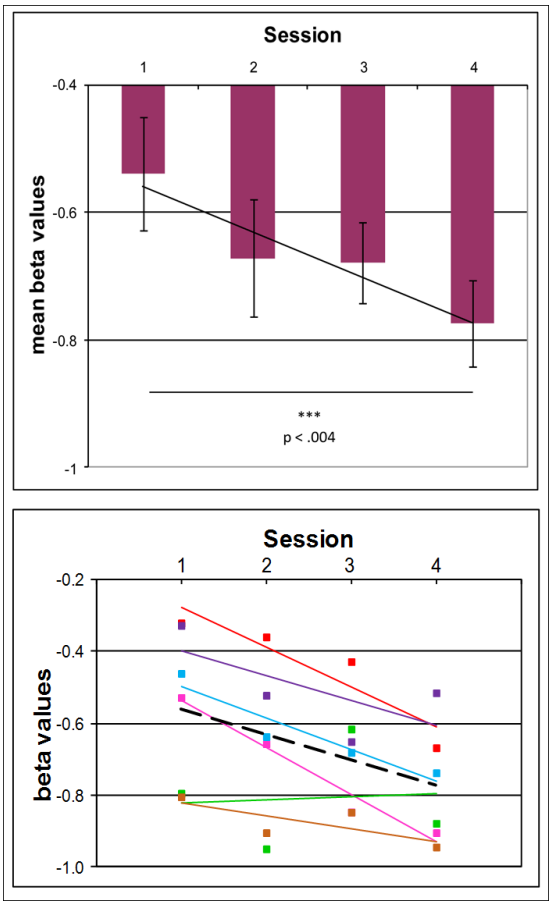

Fig2. Effect of real-time fMRI neurofeedback training over 4 sessions in the right amygdala
Increasing ability to down-regulate amygdala activity during stimulation with negative facial expressions, a) in the whole group (mean + standard deviation), b) individual values and trend-lines (black dotted line: trend-line). Given are the beta-weights of the contrast "view > regulate".

The main limitation of this study is the lack of a control group performing only emotion regulation without contingent feedback. Therefore, we cannot exclude that some of the effects are due to the repeated exertion of cognitive control. Such investigations will be conducted in future studies. Furthermore, due to the proof-of-concept character of this study, we have not tested the transfer of the learned abilities to another situation or task. This will be part of future

studies as well. Further limitations are the small number of subjects and the lack of behavioral measures, which was justified due to the main goal of a) proving feasibility and the concept of real-time neurofeedback assisted down-regulation of amygdala activity during stimulation with negative facial expressions and b) proving a training effect of repeated neurofeedback training sessions. Another limitation of this study is the lack of measures of the actual gaze direction and of physiological measures such as breath and heart rate. Prior studies have particularly shown influences of breathing on BOLD responses (Birn et al., 2009) which could have a confounding effect in our paradigm. Furthermore, measuring gaze during the task using eye-tracking techniques could ensure that participants did not influence amygdala activity by changing gaze. However, negative facial expressions, particularly of fear and anger, have been shown to activate the amygdala reliably even if presented subliminally. We have tried to overcome this problem by giving the feedback on both sides of the stimuli and by instructing the participants to focus on the centers of the faces, where furthermore the eyes are positioned as most biologically significant parts of the face (Kret et al., 2013). A marked diversion of gaze would in addition have resulted in reduced activation in the primary visual cortex and also in the left amygdala (which was both not found in the current study). In addition, we cannot completely rule out that subjects possibly changed their centre of focus away from the faces and towards the feedback stimulus. However, such processes might possibly have taken place in a similar way in the view condition. The rather quick change of the faces should furthermore have attracted the attention and visual focus back to the stimuli.

As such, this pilot study is the first combining stimulation and feedback of the amygdala with the instruction to use emotion regulation strategies to reduce amygdala activity. This approach more closely resembles emotion regulation in emotionally activating or even stressful situations than previous studies aiming at up-regulating amygdala activity (Posse et al., 2003; Zotev et al., 2011). Future studies should address aspects of "dosage" (duration and number of sessions) of rtfMRI neurofeedback and optimal integration into established therapies. Furthermore, more extensive research on the question of lateralization of amygdala activation and regulation is necessary, because the available data on lateralization of emotion processing in healthy participants and in patients with affective disorders are not compelling.

Thus, our study introduces the concept of supporting amygdala regulation during stimulation with rtfMRI neurofeedback. Our data support the further development of rtfMRI neurofeedback for improving amygdala regulation as tool for training emotion regulation in affective disorders. It could be used as add-on supporting psychotherapy particularly of affective, anxiety and emotion regulation disorders by improving, focusing, and consolidating individually effective emotion regulation strategies.

4. GENERAL DISCUSSION

4.1 SYNOPSIS

The current thesis contributes to the understanding of the neurobiological mechanisms of emotion dysregulation in BPD and how these might be targeted by specific treatment interventions using a neurobiological approach. To this end, three studies were performed. The first two investigations emphasized on the basic understanding of dysfunctional emotion processing circuits in BPD, whereas the third study focused on the methodological development of a supplemental treatment alternative for patients suffering from poor emotion regulation. While *Study 1* investigated the neurobiology of anticipatory processes prior to actual stimulus exposure, *Study 2* addressed the neural mechanisms behind purely internal mental self-referential processes of making oneself aware of current emotions in comparison to cognitive self-reflection and their significance for clinical applications using mindfulness techniques. *Study 3* served as a proof-of concept study, testing and validating the effectiveness of training self-control of amygdala activity using real-time fMRI neurofeedback during stimulus confrontation in healthy subjects, with the objective to potentially apply the method to individuals with BPD. In the next section, the main results of the included research articles will be summarized and discussed. Subsequently, the common ground of the current studies together will be argued in a broader context followed by future implications, limitations, and an overall conclusion.

4.2 MAIN FINDINGS

In *Study 1* we were interested in whether neural alterations of emotion processing in BPD occur not only during the confrontation with emotional stimuli (e.g. Hazlett et al., 2012; Herpertz et al., 2001; Koenigsberg et al., 2009b; Minzenberg et al., 2007), but already during the *anticipation* of emotional pictures, i.e. in the absence of concrete stimuli. Results demonstrate that already anticipatory processes, preceding a visual affective stimulation, are altered in BPD on the neurobiological level. Neural differences between patients with BPD and healthy participants were especially prominent during the anticipation of negative and potentially negative pictures indicating a negative emotional bias. Reduced signal change in areas associated with the cognitive aspects of emotion processing and increased activation patterns in the pregenual ACC and in the visual cortex during the emotional anticipation in BPD patients suggest a deficit in cognition-emotion interaction and a visual hyper-sensitivity towards emotional cues. Moreover, our data indicate that BPD patients may be more prone to engage in autobiographical self-

reference as they activated the PCC region (Bremner et al., 1999), although no self-related stimuli were presented. Overall, biased and dysfunctional anticipatory cognitive-emotional processes may play an important role in the psychopathology of BPD.

Study 2 examined the neurobiological correlates of introspection for one's own present feelings, within the framework of a short mindful intervention, in contrast to cognitive self-reflection in BPD patients compared to healthy individuals. As a main finding, BPD patients demonstrated difficulties in distinguishing between emotional and cognitive aspects of self-relevant information on the neural level. Such merging processes between self-related emotions and cognitions in patients with BPD might interact with the efficacy of mindfulness practice. Nevertheless, present data provide support for the concept of mindful awareness as a useful treatment intervention in terms of a down-regulation of amygdala activity in BPD, as has been shown previously in healthy participants (Herwig et al., 2010b). Yet, more research is necessary on this topic.

Study 3 was intended to develop a tool enabling subjects to train successful emotion regulation by means of real-time fMRI neurofeedback. We selected the amygdala as the target region for learning self-control, as this brain area typically is overactive in affective disorders, including in BPD (Etkin and Wager, 2007; Kraus et al., 2009; Kraus et al., 2010; Phan et al., 2002; Phillips et al., 2003a; Phillips et al., 2003b; Schmahl and Bremner, 2006). So far, real-time fMRI studies have trained participants to increase activity of a circumscribed brain area, in terms of up-regulation (insula: Caria et al., 2010; Caria et al., 2007; ACC: deCharms et al., 2005; Weiskopf et al., 2004b, motor cortex: deCharms et al., 2004; Yoo et al., 2008, sensorimotor cortex: Minati et al., 2012, sensory cortex: Haller et al., 2010, and prefrontal regions: McCaig et al., 2011). In psychiatric disorders involving heightened emotional arousal, however, down-regulation of the amygdala appears to be more clinically relevant. Therefore, in our paradigm participants trained to down-regulate their activity of the right amygdala while being confronted with specific stimulation, in this task negative emotional faces. The activity in the functionally-defined region was used as online visual feedback in six healthy subjects, who were instructed to decrease the signal by using reality checking or mindful awareness as emotion regulation strategies. Over a period of four training sessions, subjects successfully down-regulated their right amygdala compared to a passive viewing condition. Our data support the concept of using rtfMRI neurofeedback for improving self-control over the amygdala in the emotional context. It provides promising implications towards clinical treatment of psychiatric disorders with affective dysregulation, thus far more research is needed in this regard.

4.3 COMMON GROUND

Study 1 and *Study 2* together provide neurobiological evidence that emotional disturbances in BPD are not necessarily linked to the confrontation with emotional stimuli only, but also occur earlier and are internally generated. In both studies, we found neural alterations in prefrontal brain areas associated with a diminished capacity for top-down control in modulating affective responses (meta-analysis: Ruocco et al., 2013), although no specific emotional stimuli were presented. On the one hand, this finding is in line with existing neuroimaging literature on this disorder (review: Mauchnik and Schmahl, 2010; O'Neill and Frodl, 2012), but also it draws additional attention to the more basic deficits in emotion processing circuits prior active emotion regulation in BPD. Results suggest that compared to healthy subjects, patients with BPD may have problems to intuitively engage in emotion regulation while awaiting a cued negative or potentially negative emotional stimulus (*Study 1*). Consequently, dysregulated preparatory mechanisms may in fact contribute to the symptomatic heightened emotional reactivity during stimulus perception (e.g. Herpertz et al., 2001). Moreover, present data from *Study 2* highlight that already pure self-related awareness of one's emotional state, in the context of mindful introspection (Herwig et al., 2010b), is linked to dysregulated top-down processes in BPD. This is in accord with clinical observations suggesting that individuals with BPD have difficulties with experiencing emotions and consequently may not be able to, first, be aware of them and, second, to control them appropriately when needed (Crowell et al., 2009; Linehan, 1993a). These results point out that a deficiency in early and automatic self-regulatory processes mediated by prefrontal regions in BPD might comprise a critical component for emotion dysregulation in this illness.

In addition to the above, we further found support for a disrupted interplay between emotional and cognitive processes in BPD, despite the lack of active stimulation. This was prominent during both tasks, yet the observation was twofold. *Study 1* indirectly demonstrated deficits in emotion-cognition interaction associated with a disturbance between ventral and dorsal prefrontal areas during negative anticipation. In *Study 2*, on the other side, inconsistencies in the neural processing between self-related emotions and cognitions indicated that mechanisms underlying emotional and cognitive self-relevance are not clearly discriminated between one another in BPD patients. Problems in self-regulation in BPD, therefore, very likely may stem from limited access to the basic interaction between emotions and cognitions as well as from dysfunctional processing of self-relevant information.

Increased and maladaptive self-reference is part of the BPD symptomatology (Lieb et al., 2004) and was central in both studies. We found more pronounced activation patterns in brain areas associated with autobiographical memory (Bremner et al., 1999) and self-reference in general

(meta-analysis: Northoff et al., 2006) in patients with BPD, even though no self-related stimuli were presented (*Study 1*), nor specific cognitive self-focus instructed (emotional introspection condition in *Study 2*). This observation fits in well with the prominent self-reference in everyday life situations in BPD and may explain a stronger emotional engagement of BPD patients compared to healthy participants. Individuals with BPD typically are more sensitive and responsive to emotional situations (e.g. Carpenter and Trull, 2013; Linehan, 1993a), while they tend to take things personally. Merging processes between self-related emotions and cognitions on the neurobiological level (*Study 2*) may therefore emphasize on the emotional dysregulation at its core. Given the difficulties that BPD patients have in modulating their affective responses (Lieb et al., 2004), it is possible that their emotional instability derives not only from excessive involvement in emotional circuits, but also from increased autobiographical aspects, in general.

On top of this, both studies demonstrated a tendency of BPD patients to increasingly activate a 'readiness-to-act' network (Koenigsberg et al., 2009b), even if no specific emotional stimulation occurred. From clinical perspective, this is not surprising as it highlights the relevance of poor impulse control typical for the disorder (Lieb et al., 2004). In *Study 1*, we observed heightened brain activity in the visual cortex as early as during negative emotional anticipation in patients with BPD compared to healthy controls. In *Study 2,* emotion introspection as well as cognitive self-reflection recruited motor- and premotor brain areas. While the latter might be largely determined by parts of a 'reflexive social processing system', the former could be modulated by an enhanced visual sensitivity towards negative cues (Koenigsberg et al., 2009b). In a broader sense, individuals with BPD appear to show hyper-attentiveness to negative emotional signals and are more sensitive towards the impulsive affinity of acting out, which is also reflected on the neural level.

Albeit many studies on BPD have revealed increased activations of the amygdala in paradigms examining either the perception of emotional stimuli or using self-referential experiments (e.g. Donegan et al., 2003; Driessen et al., 2004; Herpertz et al., 2001; Limberg et al., 2011), we did not find statistical differences in this brain region between patients and controls in either task. In *Study 1*, this could be due to variations in task methodology and stimulus specificity, but also it might have been influenced by sample characteristics (meta-analysis: Ruocco et al., 2013). A similar regulating effect on the amygdala in patients compared to controls during the emotion introspection condition in *Study 2*, in fact could foster the concept of mindful awareness as a promising treatment option (Goodman et al., 2014; Kliem et al., 2010; Linehan, 1993a; Linehan et al., 2006). Yet, this result should be interpreted carefully, especially so, given that BPD patients overall demonstrated amygdala down-regulation irrespective of condition, which could possibly due to dissociative interference.

Taken together, *Study 1* and *Study 2* suggest that dysfunctional neurobiological aspects of basic self-regulation play a central role in BPD. Deficits in early and automatic self-regulatory processes mediated by prefrontal brain regions may contribute to the overall problems in emotion regulation. Likewise, these difficulties may derive from limited interaction between emotional and cognitive components as well as from altered processing of self-relevant information. We observed that neurobiological processes between emotions and cognitions are not clearly differentiated in BPD, which matches clinical observations of the disorder. This reduced differentiation between cognitive and emotional processes could be indeed the point where mindfulness training exerts its therapeutic effects in BPD. Our data support treatment interventions using mindfulness techniques to reduce emotional arousal in terms of amygdala down-regulation in BPD (*Study 2*). Results of both studies further indicate that individuals with BPD may be more prone to dysregulated behaviors as they demonstrated increased attentiveness of negative emotional signals as well as enhanced 'readiness-to-act', on the neural level. Above all, findings from *Study 1* and *Study 2* suggest that the neurofunctional mechanisms underlying poor self-regulation in BPD might benefit from applying a neurobiological approach using real-time fMRI neurofeedback.

Up to now, there is a growing body of literature demonstrating the effectiveness of real-time fMRI neurofeedback in self-regulation of different brain regions in healthy participants (Caria et al., 2012). However, only a small number of studies have examined this method in patient populations. Little is known about the capability of patients with psychiatric disorders to improve self-regulation of local brain activity by means of real-time fMRI neurofeedback training and their particular behavioral influence. To date, studies that have shown therapeutic effects in this regard include for instance research on chronic pain patients (deCharms et al., 2005), schizophrenia (Ruiz et al., 2013b), tinnitus (Haller et al., 2010), depression (Linden et al., 2012), or on nicotine addiction (Li et al., 2012). To address the gap between therapeutic real-time fMRI neurofeedback and psychiatric disorders suffering from disturbed affective processing, as for instance BPD, *Study 3* included in this thesis was designed to develop and examine the feasibility of using online neurofeedback to help individuals in self-control of amygdala activity.

In *Study 3* healthy participants trained to reduce their amygdala activity by applying emotion regulation strategies including reappraisal (Herwig et al., 2007b) or mindful attention and awareness (Herwig et al., 2010b), while they were stimulated with negative emotional faces. This approach is representative of daily real-life situations imposing that the amygdala is activated by external stimuli. In such cases, individuals usually automatically regulate their emotions and their amygdala, respectively. When designing this study, we considered that repeated and increasingly more effective training by real-time fMRI neurofeedback could result

in strengthening connections between brain regions implicated in emotion regulation. Results demonstrated that repeated training successfully improved the subjects' ability to down-regulate their own amygdala activity. Enhanced down-regulation across all four sessions infers a specific training effect of the neurofeedback. Although we observed increased top-down control by prefrontal areas, including the DMPFC, when applying emotion regulation strategies, this outcome was not consistent across all sessions. Along with that, no changes in connectivity between DMPFC and amygdala over the four time points were found. On the one hand, this could perhaps be explained by the individually different and adapting strategies used, but also it could be due to the limited power of the study.

Study 3 focused on feasibility features, mainly in regards of amygdala down-regulation. We were able to introduce the concept of amygdala down-regulation during stimulation with real-time fMRI neurofeedback. Yet, this study does not fully provide sufficient evidence to support the assumption that a central emotion network is involved in training self-regulation. Nevertheless, our data promote further progress of this method as a tool for training emotion regulation in psychiatric disorders in the emotional setting. It has potential to be applied in patient populations suffering from emotion dysregulation, as for instance it is the case in patients with BPD. It could be used as add-on psychotherapy by improving subjectively effective emotion regulation strategies.

4.4 IMPLICATIONS FOR FUTURE RESEARCH

Results of all three studies included in this thesis show clinical relevance for psychotherapy training in BPD. *Study 1* and *Study 2* highlight that for BPD patients, learning to become aware of current emotions and feelings and consequently regulating those appropriately before actual emotional confrontation, could be of advantage in dealing with daily affective situations. In the course of psychotherapy, patients could train to develop more attentiveness towards affective cues already prior to an emotional situation. In this way, they could learn to better cope with their inner tensions and thus would be able to anticipate following emotional reactions more properly. Future research should pay increased attention to mindfulness training in BPD, specifically emphasizing on mindfulness deficits to begin with. This may provide better treatment effectiveness in this disorder. Especially, central focus should be put on the distinction between thoughts, feelings and emotions and how these are experienced subjectively. In this context, it would be of interest to investigate whether neurobiological differentiation between emotions and thoughts would improve with successful treatment outcome. More research is

needed on the neural mechanisms underlying self-related awareness in BPD, also with regard to additional emotional stimuli.

Findings from *Study 3* demonstrate the potential of real-time fMRI neurofeedback as an add-on therapy in psychiatric disorders with disturbed affective processing. As the method reaches progress, it is reasonable to apply it in patients with BPD. Hereby, it would be interesting to examine self-control of the amygdala, while performing pure mindful self-focused attention as an emotion regulation strategy. This is especially of interest as mindfulness elements have shown neural effects (Goodman et al., 2014). Results from *Study 2* also support a mindful-close approach in form of emotion introspection with a diminishing effect on the amygdala. Patients with BPD could train emotion regulation over several different time points with the objective to improve mindfulness skills and subsequently transferring it to daily life situations.

Moreover, future studies should take a closer look into the mechanisms of top-down regulation mediated by the PFC. As *Study 1* and *Study 2* demonstrated reduced prefrontal activations associated with emotion dysregulation in BPD, it would make sense aiming at strengthening the regulation system with real-time fMRI neurofeedback. In this regard, feasibility of gaining control over high-level prefrontal regions through real-time fMRI training has been shown previously (McCaig et al., 2011). On another note, rather than targeting specific regions of dysfunction, addressing the fronto-limbic network may be even more beneficial in BPD. In this way, the disconnection between bottom-up emotional reactivity and cognitive top-down control (Cullen et al., 2011; New et al., 2012) as well as the disrupted interplay between emotional and cognitive processes in BPD could be targeted. An additional avenue in future research may lie in further study of regulating connectivity within and between the networks through real-time fMRI neurofeedback (Niv, 2013). This could lead to the development of a potential instrument in treating BPD psychopathology.

4.5 LIMITATIONS

4.5.1 Limitations Study 1 and Study 2

One restrictive aspect of both studies encompasses the lack of a behavioral control. We chose this approach to avoid interferences with executive processes (*Study 1*) and to postulate purely mental effort applicable in every-day life situations (*Study 2*). Both tasks have been performed reliably in several prior studies (e.g. Herwig et al., 2007a; Herwig et al., 2007b; Herwig et al., 2010b) and are, to our view, suitable for examining the neurobiological mechanisms in BPD. Another limiting factor of the current studies could be that we investigated rather heterogeneous patient samples with regard to comorbid diagnoses and medication. We included patients taking medication and patients with co-occurring disorders for reasons of representing a typical group of patients with BPD symptoms. Co-occurring psychiatric symptoms and disorders (Gunderson et al., 2008) are very frequent and even typical in BPD. While studying an unmedicated sample could have avoided possible confounds due to medication (Windischberger et al., 2010), it would have meant to investigate a less severely ill and less representative sample of BPD patients. Moreover, we did not assess impulsivity explicitly, which restricts our interpretation for the observed neurobiological substrates of for instance a 'readiness-to-act' network.

4.5.2 Limitations Study 3

Aside of the study-specific drawbacks that are discussed in the respective paper, more general limiting aspects regarding the real-time fMRI neurofeedback method are worth mentioning. Although the real-time fMRI technique has advanced over the past decade, various technical and methodological issues concerning signal acquisition and analyses need to be considered as they can influence the data tremendously (e.g. Caria et al., 2012). One major problem is to ensure that the feedback signal corresponds to the actual neural activity measured, rather than underlying physiological and movement artifacts, which is highly relevant for training self-regulation (Sulzer et al., 2013a). As another critical point, one must be certain that subjects are able to first discriminate the signal changes reflected by the feedback, and secondly that they are able to adapt with the temporal delay between neural and feedback signal. Hence, appropriate instructions make up a central component of neurofeedback learning (Birbaumer et al., 2008). If the subjects are properly trained and instructed, they may adapt well to the procedure (Wolpert et al., 1998). What is more to consider using real-time fMRI neurofeedback for training self-regulation is that potential behavior effects that are acquired throughout the sessions should be transferred to everyday life (e.g. deCharms et al., 2004; Ruiz et al., 2013a; Sulzer et al., 2013a). This especially holds for clinical applications, as the main goal should be to preserve the learned

skills acquired during real-time fMRI experiments, even outside the scanner. Thus, in regards to our study (*Study 3*), this will be part of future research. In general, real-time fMRI neurofeedback training has the potential to provide more causal knowledge about the functional roles of specific brain regions and their behavioral consequences, however, it still may be more susceptible to technical issues compared to other methods.

4.6 CONCLUDING REMARKS

In conclusion, the findings reported in this thesis are well supported by previous literature showing neurobiological alterations underlying emotion dysregulation in BPD (e.g. review: Mauchnik and Schmahl, 2010). At the same time, they elucidate that deficits in basic self-regulation in BPD are not limited to the confrontation with emotional stimuli only, but that they occur earlier and are internally generated, which can be observed on the neurobiological level. Current data substantiate the concept of mindfulness for treatment interventions in patients with BPD. Further, present results provide possible biological markers for disorder specific correlates as targets for treatments in BPD using a neurobiological approach.

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IV. APPENDIX

SUPPLEMENTARY MATERIAL OF STUDY 1

Online Resource 1

Whole-brain group differences (BPD > HC) during the perception of emotional stimuli

Anatomic Region	Lat	BA	Cluster size mm³	Peak Talairach coordinates x	Y	z	t-max	p-max
a) *Perception of negative stimuli > Perception of neutral stimuli*								
Inferior frontal gyros/ Insula	L	13	8742	-40	22	6	-6.8	.000000
Inferior parietal lobe	L	40	1555	-68	-38	30	-4.6	.000049
Inferior frontal gyrus/ Insula	R	13	7246	41	19	6	-5.1	.000011
Medial frontal gyrus	R	10	939	14	43	12	4.3	.000122
b) *Perception of positive stimuli > Perception of neutral stimuli*								
Inferior frontal gyrus	L	13	887	-43	22	6	-4.0	.000325

Random effects (rfx) group analysis (BPD > HCS) of brain activity during perception of emotional pictures vs. neutral pictures. Activated areas with a voxel-wise threshold of $p < .005$ are given. a) Perception of negative stimuli > perception of neutral stimuli were greater in the BPD group compared to the control group. Minimum cluster size for global error probability of $p < .05$: 803 mm³ (30 functional voxel). b) Perception of positive stimuli > perception of neutral stimuli. Minimum cluster size for global error probability of $p < .05$: 648 mm³ (25 functional voxel). Abbreviations: BA = Brodmann area, Lat = Lateralization, R = right, L = left.

Online Resource 2

Intercorrelations of questionnaires in the patient group (Pearson's *r)*

Questionnaires	HAMD	MADRS	BDI	BSL-23	DSS-4
HAMD	---	.85***	.71**	.55*	.61*
MADRS	.85***	---	.87***	.77***	.79***
BDI	.71***	.87***	---	.77***	.87***
BSL-23	.55*	.77***	.77***	---	.79***
DSS-4	.61*	.79***	.87***	.79***	---

*$p < .05$; **$p < .01$; ***$p < .001$

Online Resource 3

ROI group analyses in the BPD group versus the HC group

ROI (Center Coordinates x, y, z)	**Cluster size mm³**	**Ang > Ant**	**Auk > Ant**	**Aps > Ant**
Amygdala R (19, -5, -17)	721	t = -.41 p = .69 (.102)	t = -.38 p = .71 (.09)	t = .02 p = .99 (.01)
Amygdala L (-19, -5, -17)	721	t = .32 p = .75 (.1)	t = .59 p = .56 (.02)	t = .32 p = .75 (.111)
V1 R (5, -86, -3)	729	t = 1.68 p = .10 (.48)	t = .15 p = .89 (.04)	t = 1.12 p = .07 (.08)
V1 L (-5, -86, -3)	729	t = 2.31 **p = .03** (.62)	t = -.34 p = .73 (.1)	t = 1.13 p = .27 (.33)
LGN R (22, -22, -4)	216	t = 0.04 p = 0.97 (.01)	t = -1.06 p = 0.30 (.3)	t = .34 p = .74 (.1)
LGN L (-21, -23,-4)	216	t = -.23 p = .82 (.07)	t = -1.80 p = .081 (.52)	t = .08 p = .93 (.02)

ROI analysis of emotion anticipation conditions *negative versus neutral* (ang > ant*), unknown versus neutral* (auk > ant), and *positive versus neutral* (aps > ant) in the BPD group compared to the control group. Significant differences are given in bold ($p < .05$). Abbreviations: V1 primary visual cortex, LGN lateral geniculate nucleus, R right, L left

Online Resource 4

Correlations between the questionnaires and the mean beta weights in the clusters (Pearson's *r)*

Beta weights of activation clusters	**Questionnaires**	
	DSS4-akut	BSL
a) *Anticipation of negative stimuli > Anticipation of neutral stimuli*		
MCC	r = .32 p= .24	r = -.11 p= .67
Dorsal ACC	r = .50 p= .06	r = -.07 p= .78
Pregenual ACC	r = .28 p= .32	r = .03 p= .91
Lingual gyrus	r = .07 p= .81	r = -.33 p= .19
Posterior cingulate	r = .10 p= .73	r = .01 p= .97
b) *Anticipation of unknown stimuli > Anticipation of neutral stimuli*		
MCC / Medial frontal gyrus	r = -.07 p= .82	r = -.27 p= .29
Precentral gyrus	r = .29 p= .30	r = -.17 p= .51
Intraparietal sulcus	r = -.01 p= .98	r = -.43 p= .09
Middle frontal gyrus/ DLPFC	r = -.25 p= .37	r = -.41 p= .10
Precentral gyrus	r = .07 p= .79	r = -.40 p= .12
Inferior temporal gyrus	r = .02 p= .96	r = -.01 p= .96

A p-value of $p<.05$, 2-tailed, was considered as significant. No significant correlations between questionnaires and clusters of brain activity were found.

SUPPLEMENTARY MATERIAL OF STUDY 2

S1

Whole-brain activations in the BPD sample

Anatomic Region	**Lat**	**BA**	**Cluster size mm³**	**Peak Talairach coordinates**			***T*-max**	***P*-max**
				x	**y**	**z**		
a) feel > think								
Superior Parietal Lobule	L	7	1234	-22	-59	57	4.84	0.000130
Supramarginal gyrus	L	40	2509	-58	-35	27	6.14	0.000008
Inferior occipital gyrus	L	19	990	-25	-68	-18	4.89	0.000117
b) feel > neutral								
Superior frontal gyrus/ Middle frontal gyrus	R	6	2003	23	19	48	-5.57	0.000028
Superior frontal gyrus/ Middle frontal gyrus	L	4/6	14657	-7	4	51	6.53	0.000004
Middle frontal gyrus	L	9	3639	-34	43	30	5.73	0.000020
Insula/ Inferior frontal gyrus	L	13/44	26522	-40	13	18	6.89	0.000002
Posterior cingulate/ cuneus	L	29	5410	-16	-38	18	7.76	0.000001
Inferior parietal lobule	R	39	7748	53	-62	27	-6.23	0.000007
Middle occipital gyrus/ Inferior occipital gyrus	L	18	3817	-35	-95	6	-6.51	0.000004
Middle occipital gyrus/ Inferior occipital gyrus	R	18	1548	26	-86	0	-5.57	0.000022
c) think > neutral								
Medial frontal gyrus/ Superior frontal gyrus/ Middle frontal gyrus	L	6	30009	-7	7	51	8.88	0.000001
Insula/ Inferior frontal gyrus	L	13/44	13460	-28	19	6	6.91	0.000002

Inferior parietal lobule/ Supramarginal gyrus	R	40	2305	44	-32	24	-6.25	0.000008
Inferior parietal lobule	R	39	6561	26	-56	36	-6.35	0.000006
Posterior Cingulate	R	31	2228	14	-32	39	-4.91	0.000112
Precuneus/ Cuneus	L	31/18	1367	-7	-65	15	4.98	0.000097
Lateral occipitotemporal gyrus	R	19	1236	44	-56	-15	-6.56	0.000004
Lateral Occipitotemporal gyrus	L	19	2905	-49	-62	0	-6.34	0.000006
Superior temporal gyrus/ Into insula	R	22/42	2458	35	-14	-3	-6.25	0.000007
Superior temporal sulcus	R	20	2323	44	-32	0	5.86	0.000015
Superior temporal gyrus	L	22/42	1061	-40	-11	-9	-5.56	0.000028
Caudate body	L		13460	-19	4	18	6.91	0.000002

Activated areas in a random effects analysis (rfx) in the BPD sample with a voxel-wise threshold of $P<0.001$. Activated minimum cluster size for global error probability (Monte Carlo correction) of $P<0.05$: a) *feel > think*. Minimum cluster threshold: 653 mm^3 (25 functional voxels), b) *feel > neutral*, cluster-threshold: 859 mm^3 (33 functional voxels), and c) *think > neutral*, cluster-threshold: 884 mm^3 (33 functional voxels). Abbreviations: BA=Brodmann area, Lat=Lateralization, R=right, L=left.

S2

Whole-brain activations in the HC sample

Anatomic Region	**Lat**	**BA**	**Cluster size mm³**	**Peak Talairach coordinates**			***T*-max**	***P*-max**
				x	**y**	**z**		
a) feel > think								
Superior frontal gyrus	L	8/9	1056	-13	43	36	-4.90	0.000116
Precentral gyrus	R	4	1096	17	-23	54	4.98	0.000098
Precuneus/ Cingulate gyrus	R	7/31	14275	14	-35	30	5.37	0.000042
Superior temporal gyrus/ Supramarginal gyrus	R	39/42	3383	66	-26	9	5.16	0.000065
Superior temporal gyrus/ Insula	R	22/52	3363	53	-8	6	5.39	0.000040
Superior temporal gyrus/ Insula	L	22/52	1826	-49	-8	6	5.02	0.000089
Superior temporal gyrus/ Supramarginal gyrus	L	39/42	2835	-58	-32	18	5.89	0.000014
Superior occipital gyrus	R	19	1453	41	-80	24	5.79	0.000017
b) feel > neutral								
Superior frontal gyrus/ Medial frontal gyrus/ Cingulate gyrus	R	6/9/ 32	6516	8	49	21	-5.31	0.000048
Superior frontal gyrus/ Medial frontal gyrus	L	6	1470	-10	7	48	5.42	0.000037
Inferior parietal lobule	R	39	1549	41	-53	24	-4.92	0.000111
Inferior occipital gyrus	L	18	1823	-43	-74	-9	-4.48	0.000286
c) *think > neutral*								
Superior temporal gyrus/ Supramarginal gyrus/ Inferior parietal lobule/ Superior occipital gyrus	R	42/52 39/40 19	30435	35	-83	30	-6.50	0.000004
Superior frontal gyrus/ Medial frontal gyrus	L	6/32	3732	-10	10	45	6.37	0.000005
Cingulate gyrus	R	31	9406	11	-35	33	-6.90	0.000002
Superior temporal gyrus	L	42/52	3257	-49	-11	0	-5.83	0.000016

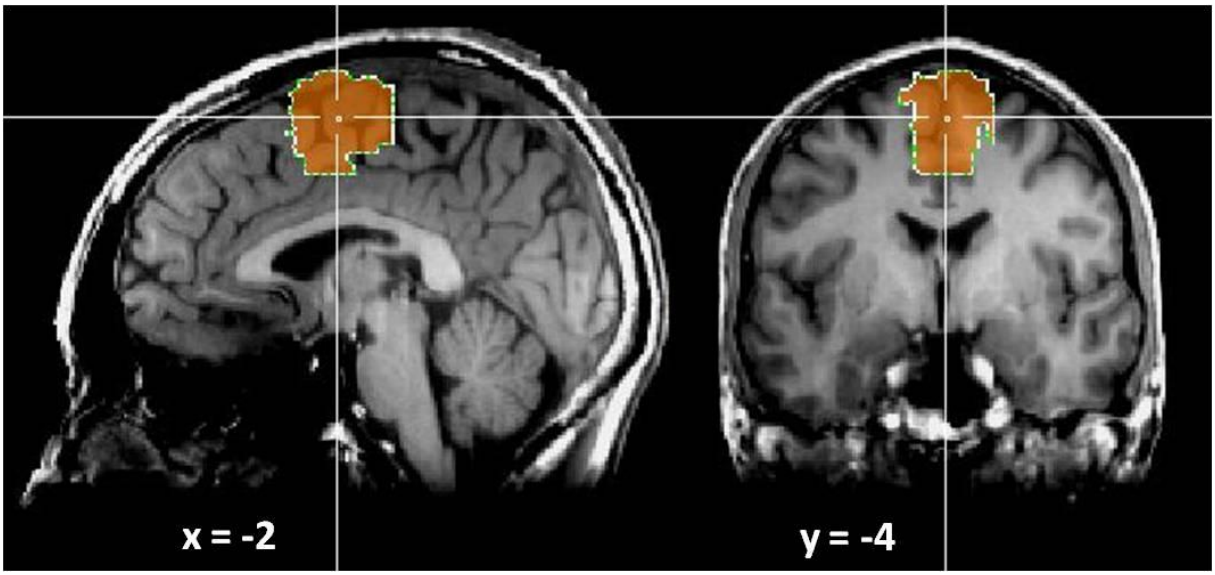
Superior temporal gyrus/ Supramarginal gyrus	L	42/40	4977	-64	-29	15	-6.22	0.000007
Medial occipitotemporal gyrus	L	20	1967	-31	-32	-18	-7.94	0.000000

Activated areas in a random effects analysis (rfx) in the BPD sample with a voxel-wise threshold of $P<0.001$. Activated minimum cluster size for global error probability (Monte Carlo correction) of $P<0.05$: a) *feel > think*. Minimum cluster threshold: 1039 mm^3 (39 functional voxels), b) *feel > neutral*, cluster-threshold: 852 mm^3 (32 functional voxels), and c) *think > neutral*, cluster-threshold: 1111 mm^3 (42 functional voxels). Abbreviations: BA=Brodmann area, Lat=Lateralization, R=right, L=left.

SUPPLEMENTARY MATERIAL OF STUDY 3

Supplementary figure S1

Overlay of all activated regions in the dorsomedial prefrontal cortex used in the analysis (summed)



CURRICULUM VITAE

Personal Information

Name	Scherpiet
Surname	Sigrid
Date/place of birth:	January 28, 1985 in Silute/Lithuania
Nationality:	German

Education

2011 – 2014	**University of Zurich, CH** **PhD thesis in Psychology** **Supervisor:** Prof. Dr. L. Jäncke
2009 – 2011	**International Max-Planck Research School,** **Eberhard-Karls University, Tuebingen, D** **M. Sc. in Neural & Behavioral Sciences**
2004 – 2008	**Northeastern University, Boston, MA, USA** **B. Sc. in Psychology, Minor in Criminal Justice** **Athletics:** Division 1 Northeastern University Women's Basketball Team
2003 – 2004	**Carlisle School-IB World School, Martinsville, VA, USA** **High School Diploma** **Athletics:** Basketball
1998 – 2003	**Sportgymnasium, Halle/Saale, D** **Athletics:** Basketball

Research experiences & internships

Since 07/2011	**University of Zurich, CH** **Psychiatric University Hospital** Research Associate: Group of Prof. Dr. U. Herwig Project: *"Neurobiology of emotion regulation and self-reference"* Methods: fMRI, real-time fMRI neurofeedback
09/2010 – 05/2011	**Institute for Medical Psychology and Behavioral Neurobiology, Tuebingen, D** Master Thesis: Group of Prof. Dr. N. Birbaumer; Supervisor Dr. R. Veit Project: *"Successful perspective taking mediates empathy for pain"* Methods: fMRI

11/2010 – 01/2011	**Hertie-Institute for Clinical Brain Research, Tuebingen, D** Department of Cognitive Neurology Intern: Group of Prof. Dr. P. Thier; Supervisor Dr. A. Lindner Project: *"Deficits in the self-attribution of agency due to parietal lesion?"* Methods: psychophysical experiments
02/2010 – 4/2010	**Hertie-Institute for Clinical Brain Research, Tuebingen, D** Department of Neuropsychology Intern: Group of Prof. Dr. H.-O. Karnath; Supervisor Dr. M. Himmelbach Project: *"Lateralization of brain activity during visual exploration"* Methods: fMRI data analyses
10/2008 – 08/2009	**Friedrich Schiller University of Jena, D** Department of Psychiatry and Psychotherapy Research Assistant – Group of Dr. I. Nenadic Project**:** *"European Twin Study Network on Schizophrenia (EUTwinsS)"* Methods: fMRI, MRI, Neuropsychological Testing
07/2008 – 09/2008	**Friedrich Schiller University of Jena, D** Department of Psychiatry and Psychotherapy Cognitive Behavioral Therapy Unit Clinical Intern, Co-therapist: Supervisor Dr. G. Peikert Group Therapy: supervisor in social competency skills, athletic trainer
01/2007 – 04/2007	**Northeastern University, Boston, USA** Faculty of Psychology Directed Study – Group of Prof. J. Hall, PhD Project: *"Patients' satisfaction with male versus female med. care providers"* Methods: meta-analysis

Achievements & scholarships

Academics

Reviewer Activity (2014)
Psychiatry Research: Neuroimaging

Student representative PhD Program Psychology (since 03/2013)
University of Zurich, CH

Research Travel Grant (11/2013)
University of Zurich, CH

Poster award (2012)
20th European Congress of Psychiatry

Dean's List (2006)
Northeastern University, Boston, MA, USA

Member of National Honor Society (2004)
Carlisle School-IB World School, Martinsville, VA, USA

Athletics

Full Athletic Scholarship (09/2004 – 05/2008)
Northeastern University, Boston, MA, USA

Full Athletic Scholarship (09/2003 – 05/2004)
Carlisle School-IB World School, Martinsville, VA, USA

Journal Publications

Scherpiet, S., Herwig, U., Opialla, S., Scheerer, H., Jäncke, L., Brühl, A.B.: *"Reduced neural differentiation between self-related cognitive and emotional processes in women with borderline personality disorder."* (submitted)

Opialla, S., Herwig, U., **Scherpiet, S.**, Hittmeyer, A., Cattapan, K., Jäncke, L., Brühl, A.B.: "*Changes in the neural networks of self-reflection and emotion introspection with remission of depression – a longitudinal study."* (submitted)

Opialla, S., Lutz, J., **Scherpiet, S.**, Hittmeyer, A., Jäncke, L., Rufer, M., Grosse Holtforth, M., Herwig, U., Brühl, A.B. "*Neural circuits of emotion regulation: A comparison of mindfulness-based and cognitive reappraisal strategies."* Eur Arch Psychiatry Clin Neurosci. (in press)

Brühl, A.B, **Scherpiet, S.**, Sulzer, J., Stämpfli, P., Seifritz, E., Herwig, U.*: "Real-time neurofeedback using functional MRI could improve down-regulation of amygdala activity during emotional stimulation: a proof-of-concept study."* Brain Topogr. 2014 Jan; 27(1):138-48

Scherpiet, S., Brühl, A.B., Opialla, S., Roth, L., Jäncke, L., Herwig, U.: "*Altered emotion processing circuits during the anticipation of emotional stimuli in women with borderline personality disorder."* Eur Arch Psychiatry Clin Neurosci. 2014 Feb; 264(1):45-60

Mingoia, G., Langbein, K., Dietzek, M., Wagner, G., Smesny, S., **Scherpiet, S.**, Maitra, R., Reichenbach, J.R., Schlösser, R.G.M., Gaser, C., Sauer, H., Nenadic, I.: "*Frequency domains of resting state default mode network activity in schizophrenia."* Psychiatry Res. 2013 Oct 30;214(1):80-2

van der Heiden, L.*, **Scherpiet, S.***, Konicar, L., Birbaumer, N., Veit, R.: "*Inter-individual differences in successful perspective taking during pain perception mediates emotional responsiveness in self and others: An fMRI study."* Neuroimage, 2013, 65: 387-94. (*both authors contributed equally)

Nenadic, I., Maitra, R., **Scherpiet, S.**, Gaser, C., Schultz, C., Schachtzabel, C., Smesny, S., Reichenbach, J.R., Treutlein, J., Mühleisen, T.W., Deufel, T., Cichon, S., Rietschel, M., Nöthen, M.M., Sauer, H., Schlösser, R.G.M.: *"Glutamate receptor delta 1 (GRID1) genetic variation and brain structure in schizophrenia."* J Psychiatr Res, 2012, 46(12): 1531-9.